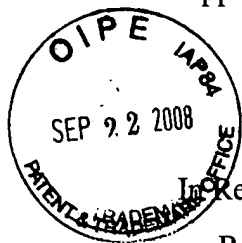


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Applic. No. 10/271,832
Appeal Brief

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

Rosenthal et al.

Serial No.: 10/728,277

Conf. No.: 7142

Filed: December 4, 2003

Atty. File No.: 42830-10010

For: "TREATMENT OF MUCOSITIS"

) Group Art Unit: 1614
)
) Examiner: Roberts, Lezah
)

) APPEAL BRIEF
) (37 C.F.R. § 41.37)
)

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Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Appeal Brief is filed in relation to appeal of the referenced Application from claim rejections stated in an Office Action dated September 20, 2007 (the "**Appealed Office Action**"), on which a Notice of Appeal was filed March 20, 2008. This Appeal Brief is accompanied by a check of \$510 for the fee required under 37 C.F.R. §1.136(a) and a check for \$1,640 for the extension fee under 37 C.F.R. §1.17(a). If any additional fees are due, please debit such fees to Deposit Account No. 50-1419. Credit any overpayments to Deposit Account No. 50-1419.

This Appeal Brief includes the following appendices:

- Appendix A – Claims;
- Appendix B – Evidence; and
- Appendix C – Related Proceedings.

REAL PARTY IN INTEREST

The real party in interest is Endo Pharmaceuticals Colorado, Inc., a Delaware corporation, by assignment to RxKinetix, Inc., an entity whose name has since been changed to Endo Pharmaceuticals Colorado, Inc.

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RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

Claims 1, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 are pending in the application.

Claims 2-14, 16, 18, 21-23, 26-30, 32-34, 36, 37, 39-132, 138, 139, 141 and 144 have been cancelled.

Claims 1, 15, 17, 19, 20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143 and 145-152 are the subject of this appeal.

Claims 1, 15, 17, 19-20, 24, 25, 31, 35, 38, 133-137, 140, 142, 143, and 145-152 are rejected under 35 U.S.C. § 1.03(a)

STATUS OF AMENDMENTS

No amendments of the claims have been filed after issuance of the Appealed Office Action, and there are no amendments to the claims that are pending.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is the only independent claim subject to appeal. Claim 1 recites a therapeutic composition useful for treatment of mucositis as a side effect of cancer therapy, and the claimed composition requires the following features:

- (i) N-acetylcysteine (*see, inter alia*, the specification at page 4, lines 4-6; page 7, lines 1-2 and 26, page 17, line 23 through page 18, line 2; page 18, lines 9-12; Examples at page 24, line 15 through page 27, line 11) in an amount effective as formulated in the composition to provide therapeutic effect for treatment of the mucositis (*see, inter alia*, the specification at page 3, line 29 through page 4, line 4; page 8, lines 17-20; page 8, line 30 through page 9, line 8; page 18, lines 18-24);

- (ii) from 5 weight percent to 20 weight percent poloxamer 407 (*see, inter alia*, the specification at page 13, line 13 through page 14, line 8; page 15, lines 10-15; Examples at page 24, line 15 through page 27, line 11);
- (iii) a carrier liquid comprising water (*see, inter alia*, the specification at page 5 lines 1-8; page 9, lines 23-28; page 19, lines 11-13; Examples at page 24, line 15 through page 27, line 11) in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart reverse-thermal viscosity behavior to the therapeutic composition (*see, inter alia*, the specification at page 4, lines 8-15; page 9, lines 21-23; page 11, lines 15-22; page 13, lines 17-19), wherein the composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C (*see, inter alia*, the specification at page 10, lines 11-15);
- (iv) wherein, at some temperature in a range of from 2°C to 8°C (*see, inter alia*, the specification at page 10, lines 15-19; page 14, lines 21-22) the therapeutic composition is in the form of an aqueous solution with the poloxamer 407 and the N-acetylcysteine dissolved in the water (*see, inter alia*, the specification at page 5, lines 4-8; page 9, line 18 through page 10, line 2).

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds for rejection are to be reviewed in this appeal:

- Ground 1: Rejection of Claims 1, 15, 17, 19, 20, 24, 25, 31, 38, 133-137, 140, 142, 143 and 145-152 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,620,428 by *Hoeck et al.* (“*Hoeck et al.*”) in view of U.S. Patent No. 4,188,373 by *Krezanoski* (“*Krezanoski*”).
- Ground 2: Rejection of 1, 15, 17, 19, 20, 24, 25, 31, 35, 133-137, 140, 142, 143 and 145-152 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,620,428 by *Hoeck et al.* (“*Hoeck et al.*”) in view of U.S. Patent No. 5,256,396 by *Piechota, Jr.* (“*Piechota*”).

ARGUMENT

I. Ground 1, 35 U.S.C. § 103(a), *Hoeck et al.* in view of *Krezanoski*, Independent Claim 1.

A. The references do not make obvious the rejected claims when the prior art is considered as a whole, and because of objective evidence of nonobviousness.

The Examiner's apparent reasoning in making the rejection is that it would be obvious to combine the teachings of the primary reference, *Hoeck et al.*, in relation to transmucosal delivery of N-acetylcysteine, with the teachings of the secondary reference, *Krezanoski*, in relation to a drug delivery vehicle for mucosal delivery, to make obvious the claimed composition. The rejected claims are, however, not obvious over *Hoeck et al.* and *Krezanoski* for at least the following reasons:

- 1) Considering the teachings of *Hoeck et al.* and *Krezanoski* in the context of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.* and *Krezanoski et al.*; and
- 2) There is persuasive objective evidence of nonobviousness in relation to significant and unexpected properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy and in relation to a long felt unsolved need addressed by the claimed composition for such a treatment, which evidence the Examiner has inappropriately refused to give any weight.

B. Based on a consideration of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.* and *Krezanoski et al.*

The teachings of *Hoeck et al.* are focused on transdermal delivery of N-acetylcysteine as a mucolytic agent, or expectorant (*Hoeck et al.*, at column 1, lines 9-30; column 2, lines 37-48; column 2, line 65 through column 3, line 4) with an objective of overcoming identified disadvantages and side effects associated with inhalation or peroral (through the mouth)

administration of the mucolytic agent (*Hoeck et al.*, at column 1, lines 31-62; column 2, lines 34-36). As a mucolytic agent, the N-acetylcysteine is used to decrease the viscosity of mucous and purulent expectorates. *Hoeck et al.*, at column 1, lines 19-24; column 2, lines 48-50; column 3, lines 2-4. Action as a mucolytic agent, however, is significantly different than and not indicative of efficacy for treatment of mucositis, as discussed in the Troha Declaration in the paragraph bridging pages 3 and 4.

Hoeck et al. disclose that transdermal delivery of N-acetylcysteine as a mucolytic agent can be accomplished from “topical products such as ointments or cremes or from transdermal devices,” and identify main categories of such transdermal devices as the “reservoir type,” “matrix type,” “drug-in-adhesive type,” and “multi-laminate type,” all of which include a structural backing and a layer including the drug in communication through the skin, either directly through contact with the skin or indirectly through an adhesive and/or membrane layer. *Hoeck et al.*, at column 3, lines 23-50; Figs. 1A-1D. A fifth category of transdermal delivery device is also mentioned, referred to as “iontophoretic type,” which uses an electrical potential gradient to transfer drug through the skin. *Hoeck et al.*, at column 3, lines 51-57. Several polymeric and other materials that might be used in various ones of the transdermal delivery devices are disclosed by *Hoeck et al.* at column 3, line 66 through column 4, line 44, and *Hoeck et al.* provide several compositional examples in working examples presented in columns 6-11. In the extensive disclosure of these administration forms, *Hoeck et al.* do not disclose poloxamer polymers, or poloxamer 407 specifically.

In contrast, *Krezanoski et al.* disclose drug delivery compositions, referred to as “pharmaceutical vehicles” that are directed generally for use to deliver drugs to a mucous membrane, with a focus on ocular applications. *Krezanoski*, at column 2, lines 49-62; column 4, lines 43-54; column 7, lines 34-52. The drug delivery compositions are aqueous solutions with about 10 to 26%, and preferably 17 to 26%, polyoxyethylene-polyoxypropylene block copolymer (poloxamer) formulated to be reverse-thermal gelling, and one preferred poloxamer is Pluronic® F-127 (a poloxamer 407). *Krezanoski*, at column 2, line 63 through column 3, line 19; column 3, line 61 through column 4, line 3; column 5, lines 14-53. Although *Krezanoski* states that “any pharmaceutically active material” may be included in the drug delivery composition, the

disclosure of *Krezanoski* is clearly directed primarily to ocular pharmaceutical applications and N-acetylcysteine is not listed among the exemplary drugs disclosed by *Krezanoski* at column 7, lines 30-52.

The motivation asserted by the Examiner for one of ordinary skill in the art to combine the N-acetylcysteine for transdermal delivery as a mucolytic disclosed by *Hoeck et al.* with the drug delivery composition of *Krezanoski* is a “desire to increase drug absorption by the mucous membrane for rapid introduction into the system, as disclosed by the secondary reference [*Krezanoski*],” apparently based on disclosures by *Krezanoski* that his drug delivery vehicle had been unexpectedly found to increase drug absorption by the mucous membrane; that the pharmacologic response had been unexpectedly prolonged; and that drug action is typically both increased and prolonged by a factor of 2 or more. Appealed Office Action at pages 3 and 4; *Krezanoski* at column 5 lines 54-61.

Hoeck et al. mention the possibility of transmucosal administration of N-acetylcysteine for a short time simultaneous with initial transdermal administration, until the transdermal administration has had time to build up a therapeutically effective serum level of N-acetylcysteine, and this transmucosal administration is temporarily “tolerated” by *Hoeck et al.* for a short time in spite of disadvantages identified with transmucosal delivery. See, the Appealed Office Action at page 3, first paragraph; *Hoeck et al.*, at column 12, lines 1-16. For this temporary transmucosal delivery, *Hoeck et al.* disclose using the same forms of administration as disclosed for transdermal delivery. *Hoeck et al.*, at column 12, lines 17-34. Therefore, *Hoeck et al.* teach that transdermal delivery of N-acetylcysteine as a mucolytic agent is preferable to transmucosal delivery, but in the event of transmucosal delivery one of ordinary skill in the art would be guided by *Hoeck et al.* to tolerate transmucosal delivery only for a short time and to use transdermal delivery devices such as those disclosed by *Hoeck et al.*, and there would be no motivation to look beyond *Hoeck et al.* for other transmucosal delivery techniques or formulations for this temporary situation. Moreover, the teachings by *Hoeck et al.* that transmucosal delivery is generally undesirable and to be “tolerated” only for a short time are teachings away from combining N-acetylcysteine with delivery compositions targeted to mucosal delivery, such as the delivery composition of *Krezanoski*.

Assuming, *arguendo*, however, that one of ordinary skill in the art would for some reason be motivated to look beyond *Hoeck et al.* for other possible compositions for transmucosal delivery there would be a multitude of possibilities of which the teachings of *Krezanoski* would be only one, and in that regard, this situation seems to be particularly susceptible to hindsight biases that should be guarded against.

KSR Int'l Co. v Teleflex Inc., ___ U.S. ___, 127 S.Ct. 1727, 167 L. Ed. 2d 705, 82 USPQ 2d 1385 (2007) recognized that “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,” but also rejected “[r]igid preventive rules that deny factfinders recourse to common sense.” However, along with a flexible, common sense approach, *KSR Int'l* also recognized and cautioned against the trap of hindsight analysis, warning that a “factfinder should be aware of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.” See, *KSR Int'l* at 127 S.Ct. 1741-1743.

With respect to this application, when the prior art is considered as a whole, there is even less of a reason for one of ordinary skill in the art to be motivated to select the drug delivery composition of *Krezanoski* from among the multitude of possibilities, and the susceptibility for hindsight biases becomes apparent. For example, among the multitude of references that would be encountered by one of ordinary skill in the art is U.S. Patent No. 6,503,955 by Dobrozsi et al. (“*Dobrozsi et al.*”), which was cited in a previous claim rejection, which has been withdrawn. Dobrozsi et al. teach away from the use of drug delivery compositions of the very type disclosed by *Krezanoski* for mucosal drug delivery. At column 2, lines 17-67, *Dobrozsi et al.* discuss reverse-thermal gelling delivery vehicle compositions of the type disclosed by *Krezanoski* made using poloxamer 407, or some other poloxamers, and problems associated with those compositions, and *Dobrozsi et al.* conclude that discussion with the following statement:

While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions.

Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments.

Dobrozsi et al. go on to disclose a very different type of drug delivery vehicle, useful for mucosal delivery applications, which they term a “pourable liquid vehicle”, and which has considerably different properties than the delivery vehicle of *Krezanoski*, even though both references disclose the use of poloxamers, including poloxamer 407. Reference is also made to the Mathews Declaration for a further discussion concerning the teaching away by *Dobrozsi et al.* from drug delivery compositions such as those disclosed by *Krezanoski*.

As another example of the references that would be encountered by one of ordinary skill in the art is U.S. Patent No. 6,316,011 by Ron et al. (“*Ron et al.*”), which is also a reference of record in this application, although not cited in the Appealed Office Action. Ron et al. specifically discuss poloxamer-based compositions for drug delivery, of the general type disclosed in *Krezanoski*, and assert there are problems with such compositions, including the relatively large concentration of polymer needed to produce a desired liquid-gel transition temperature, a typically very viscous nature even when in a “liquid” phase, and that the high concentrations of polymer may cause unfavorable physiological interactions during use. In the face of these asserted shortcomings, *Ron et al.* propose a different type of composition for drug delivery, which uses a particular linear block copolymer made by end-modifying a polyoxyalkylene, such as a poloxamer, with a bioadhesive polymer, which may be poly(acrylic acid). See, *Ron et al.* at column 2, lines 28-44; column 3, lines 48-57; column 3, line 66 through column 4, line 17.

Therefore, one of ordinary skill in the art considering the prior art as a whole would not be led to a combination of *Hoeck et al.* with *Krezanoski* as asserted by the Examiner, especially when considering the teachings away by *Hoeck et al.*, *Ron et al.*, and by *Dobrozsi et al.* Although *Dobrozsi et al.* and *Ron et al.* are not cited for a claim rejection in the Appealed Office Action, the teachings away in references such as *Dobrozsi et al.* and *Ron et al.* are still relevant to show that it would not be obvious to one of ordinary skill in the art to select the drug delivery composition of *Krezanoski* for combination with *Hoeck et al.*, especially because *Hoeck et al.*

already provide significant guidance on suitable drug delivery compositions. Based on the guidance provided by *Hoeck et al.* of suitable composition for transdermal delivery, the teaching away by *Hoeck et al.* of transmucosal delivery, other teachings away in the prior art (e.g., *Dobrozsi et al.*, *Ron et al.*) from the use of drug delivery vehicles of the type disclosed by *Krezanoski*, and a common sense recognition that there are a multitude of possibilities for drug delivery compositions, one of ordinary skill in the art would not find obvious a combination of N-acetylcysteine as a mucolytic agent for topical delivery as disclosed by *Hoeck et al.* with the drug delivery composition disclosed by *Krezanoski*. A finding otherwise would appear to be based on a hindsight bias in selectively picking particular disclosures of *Krezanoski* without regard to the teachings of the prior art as a whole.

C. In determining whether claimed subject matter is nonobvious, all objective evidence submitted to rebut a case of obviousness must be considered.

Assuming, *arguendo*, that the Examiner has made a *prima facie* showing of obviousness, based on *Hoeck et al.* and *Krezanoski*, that would raise only a presumption of obviousness, which could be overcome by submission of appropriate rebuttal evidence, and all such rebuttal evidence must be considered in determining the question of patentability. *In re Dillon*, 919 F.2d 688, 692-693, 16 USPQ 2d 1897 (Fed. Cir. 1990). Such evidence may be directed to the so-called secondary considerations, such as “commercial success, long felt but unsolved needs, failure of others, etc.” in the approach to analyzing nonobviousness set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 86 S. Ct 684, 15 L. Ed. 2d 545, 148 USPQ 459 (1966). *KSR Int’l* reaffirms the basic approach set out in *Graham* for evaluating a claimed invention relative to the prior art and with consideration to such secondary factors. *KSR Int’l* also recognizes, for example, that combinations of known elements may be nonobvious when there is a teaching away from the combination, or when the combination creates some new synergy, or when the combination yields more than predictable results. *KSR Int’l* at 127 S.Ct. 1739-1740, citing, respectively, to *United States v. Adams*, 383 U.S. 39, 86 S. Ct 708, 15 L. Ed. 2d 572, 148 USPQ 479 (1966); *Anderson’s-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S.

57, 90 S. Ct. 305, 24 L. Ed. 2d 258, 163 USPQ 673 (1969); and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784, 189 USPQ 449 (1976). Finding *Sakraida* and *Anderson's Black Rock* to be illustrative, the Court in *KSR Int'l* noted that “a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR Int'l*, at 127 S. Ct. 1740. In assessing whether an invention is nonobvious all rebuttal evidence that is submitted must be considered, including all evidence of unexpected properties of a composition, and including unexpected biological or pharmaceutical properties of the composition. *Sullivan v. Russell*, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007); *In re Papesch*, 50 C.C.P.A. 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

D. The application specification and the Troha Declaration provide significant evidence of (a) an unexpected property of the claimed composition in relation to efficacy for treatment of oral mucositis as a side effect of cancer therapy and (b) a long felt but unsolved need for such a treatment that is addressed by the claimed composition, which evidence, together with the noted deficiencies in *Hoeck et al.* and *Piechota* discussed above, effectively rebuts any case of obviousness based on *Hoeck et al.* and *Krezanoski*.

The Background Of The Invention Section on pages 1-3 of the application specification discuss the serious nature of mucositis as a side effect of cancer therapy, with particular emphasis on oral mucositis. Prior approaches to treatment of oral mucositis are discussed, and it is stated that “[t]o date, none of these approaches has shown significant impact”, and that “[g]iven that a large number of patients suffer annually and patients undergoing cancer therapy often receive multiple cycles of chemotherapy and/or radiation therapy, there is a significant need for improved treatment of mucositis.” See, the application specification at page 3, lines 16-17 and 23-25. On pages 2-3, the Troha Declaration presents additional discussion concerning the serious nature of oral mucositis as a common and often debilitating side effect of cancer therapy, that the incidence of severe oral mucositis is high in patients with head and neck cancer who receive high doses of radiation as part of their cancer treatment, and that for such patients there was no treatment

approved by the United States Food and Drug Administration. The Troha Declaration also states that the occurrence of severe oral mucositis can significantly negatively impact the successful completion of cancer therapy, and that there is a significant need for an oral mucositis treatment for cancer therapy patients. The application specification and the Troha Declaration, therefore, provide significant evidence of a long felt but unresolved need for a treatment for oral mucositis as a side effect of cancer therapy.

One pages 5-8 of the Troha Declaration, results are presented of an animal study conducted on hamsters concerning the use of N-acetylcysteine as an active agent to treat oral mucositis resulting from irradiation. Compared are four of the five compositions that are shown in the Example presented on pages 24-27 of the application specification. One of these four compositions is within the scope of the claims on appeal and three are not within the scope of the claims on appeal. The procedure for preparation of the compositions is described in the Example, on page 24 of the specification. A composition within the scope of the rejected claims (referred to both as A2.02 and RK-0202) contained 10 weight percent N-acetylcysteine formulated with 16.25 weight poloxamer 407 (in the form of Pluronic® F-127 product from BASF Corporation) formulated in a water solution. Another composition (referred to both as A2.03 and RK-0203) also contained 10 weight percent N-acetylcysteine, but was formulated in water without the poloxamer 407. The other two compositions were control formulations containing no N-acetylcysteine. One of the control formulations (referred to as the vehicle control) contained 16.25% of the poloxamer 407, but no N-acetylcysteine. This composition also contained a small amount (0.5%) of chitosan, a penetration enhancer that was also under investigation for use with N-acetylcysteine delivery. The other control formulation was a water control, with no poloxamer 407 and no N-acetylcysteine.

As demonstrated in the Example section of the specification, and as discussed further in the Troha Declaration, the A2.02/RK-0202 composition formulated with both the N-acetylcysteine and the poloxamer 407 significantly outperformed the other compositions, including the A2.03/RK-0203 composition that contained the N-acetylcysteine in water without the poloxamer 407. Exhibit B of the Troha Declaration includes a tabulation of oral mucositis scores assigned to hamster groups for the four test compositions and Table D-4, on page 9 of the

Troha Declaration, summarizes severe mucositis incidence for each hamster group from the data in Exhibit B. As discussed on page 8 of the Troha Declaration, the data summarized in Table D-4 shows significant differences between the A2.02/RK-0202 composition and the A2.03/RK-0203 composition, including both a significant reduction in the incidence of severe mucositis and a delay in the onset of severe mucositis. Moreover, the Troha Declaration states that this result would not be expected due simply to the change in delivery vehicle (from the formulation without to the formulation with the poloxamer 407). Also, the vehicle control and water control compositions performed significantly worse than either of the formulations containing N-acetylcysteine.

On pages 10-14, the Troha Declaration also summarizes information from a phase 2 clinical trial of patients undergoing radiation therapy for cancer, and involving compositions formulated with 5% or 10% N-acetylcysteine and 13% poloxamer 407. Due to a higher effect with the 10% formulation, the 5% formulation was eliminated through interim analysis. The Troha Declaration summarizes a comparison of performance of the formulation with 10% N-acetylcysteine and 13% poloxamer 407 with placebo, showing a significant reduction in the incidence of severe oral mucositis. On page 14, the Troha Declaration does state that the FDA has designated the 10% N-acetylcysteine composition of the phase 2 clinical trial as qualifying for Fast Track status because it was being investigated for reduction of severe oral mucositis, further demonstrating that the claimed composition addresses a long-felt but unsolved need for treating oral mucositis as a side effect of cancer therapy.

Therefore, the application specification and the Troha Declaration provide significant evidence of at least the following:

- (1) Poloxamer 407 formulated in water does not have efficacy for treatment of oral mucositis.
- (2) N-acetylcysteine has efficacy for treating oral mucositis;
- (3) The efficacy of oral mucositis treatment with N-acetylcysteine can be increased by a significant and surprising amount when formulated with the poloxamer 407 in a composition of the rejected claims relative to formulation of N-acetylcysteine in water; and

- (4) Oral mucositis is a serious problem for certain cancer patients undergoing radiation therapy, and there is a long-felt but unresolved need for a treatment for such oral mucositis and the claimed composition can address that need.

E. The Examiner erred in not giving any weight to the objective evidence of nonobviousness that the claimed composition has an unexpected property in relation to effectiveness for treatment of oral mucositis and as addressing a long felt but unresolved need for such treatment.

Evidence presented in the application specification and the Troha Declaration show that the claimed composition has a property, unexpected from the prior art, of being effective for treatment of oral mucositis as a side effect of cancer therapy, and that the claimed composition addresses a long felt but unsolved need for such a treatment.

On page 11 of the Appealed Office Action, the Examiner discusses the Troha Declaration with respect to the obviousness rejections in the Appealed Office Action. In that section of the Office Action, the Examiner makes no mention of any consideration of the performance data presented and discussed in the Troha Declaration or in the application specification in relation to evidence of unexpected properties or evidence of addressing a long felt but unsolved need. However, on pages 4 and 5 of the Appealed Office Action, in making the rejection based on *Hoeck et al.* and *Krezanoski*, the Examiner states:

In regards to the intended use of the compositions of the combined reference [sic], intended use carries no weight in determining patentability because the compositions of the combined references are substantially the same as those of the instant claims and therefore should be able to treat mucositis, because the compositions of the reference [sic] and the compositions of the instant claims are substantially the same.

Also, on page 10 of the Appealed Office Action, discussing the Troha Declaration in relation to prior claim rejections that were withdrawn, the Examiner states:

The [Troha] Declaration is based on the intended use of the recited compositions and does not show a side-by-side comparison with the compositions of the cited references. This type of argument may have been considered effective if the claims were drawn to a method and not a composition . . . It [the Troha Declaration] does not show that the compositions of the references don't have the same capabilities or show unexpected results in view of the compositions of the references.

It is respectfully submitted that these cited statements, and the lack of consideration given to the Troha Declaration and the conclusions drawn from that declaration, are incorrect and not in conformance with controlling legal precedent.

The *Papesch* case, cited above, is particularly applicable to the situation here, because the court in *Papesch* specifically rejected reasoning similar to that expressed by the Examiner in the Appealed Office Action, that evidence of unexpected pharmacological properties, although perhaps relevant to method of use claims is not relevant to composition claims. In *Papesch*, the Court of Customs and Patent Appeals confronted a situation where the invention was to a new compound that was structurally similar to a prior art compound, but the compound of the invention possessed potent anti-inflammatory activity in contrast to a structurally related prior art compound. In *Papesch*, the court rejected reasoning very similar to that proposed by the Examiner here for discounting the evidentiary value of the Troha Declaration, and held that evidence of an unexpected biological or pharmaceutical property can overcome an obviousness rejection based on structural similarity.

In the facts of *Papesch*, the examiner rejected claims to the new compound as being obvious over a prior art reference disclosing a closely related, structurally similar homolog. In responding the rejection, the applicant submitted an affidavit showing that the new compound had the potent anti-inflammatory activity. In maintaining the rejection, the examiner made the following statement, quoted in *Papesch*:

The affidavit is interesting but irrelevant to the rejection since it is not directed to the subject matter “sought to be patented”, namely, the use in the arts of the compounds. The obvious compound is not made less obvious by its properties in an art use. [*Papesch*, at 315 F2d. 383-384, quoting the examiner.]

The court in *Papesch* summarized the essence of the Examiner’s obviousness rejection, citing to the following quotation:

The homologous compound being obvious it is not seen how it can become less obvious, as a compound, merely by discovering that in addition to the community of common physical and chemical properties expected of members of an homologues [sic] series it also has other improved or valuable properties. Such discovery is not proper support for a patent for the compound per se. [*Papesch*, at 315 F.2d 385, citation omitted.]

The applicant appealed the rejection, which rejection was affirmed by the Appeals Board. The court in *Papesch*, considering the Board’s record in affirmation of the rejection, found that the Board had not given weight to the affidavit evidence of unexpected anti-inflammatory activity, because the property was a pharmacological property. The court in *Papesch* reviewed the case law involving evidence of unexpected properties to overcome a finding of obviousness, and in overturning the board and the examiner’s rejection of the claim the court stated:

From the foregoing cases it will be seen that this and other courts, both before and after the enactment of *section 103*, have determined the unobviousness and patentability of new chemical compounds by taking into consideration their biological or pharmacological properties. Nine of the ten cases above considered, directly and indirectly, involved such properties. Patentability has not been determined on the basis of the obviousness of structure alone. In fact, where patentability was found in the above cases it was found in spite of close similarity of chemical structure, often much closer similarity than we have here.

Returning now to the decision of the board in this case, we think that it rests on one fundamental error of law, namely, the failure to take into consideration the biological or pharmaceutical property of the compounds as anti-inflammatory agents on the ground that to chemists the structure of the compounds would be so obvious as to be beyond doubt, and that a showing of such properties is to be used only to resolve doubt.

From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. [*Papesch*, at 315 F.2d 391, underlining added for emphasis.]

In *Dillon*, the CAFC sitting *en banc* cited to and specifically approved of the holding in *Papesch*. *Dillon*, at 919 F.2d 697. The post *KSR Int'l* case of *Sullivan*, cited previously, is also instructive. *Sullivan* involved a situation similar to that here where a claim was rejected with no weight being given to evidence of unexpected properties of a composition on the asserted basis that such evidence was directed to an intended use of the claimed composition and that no weight could be given to the intended use of a composition. The court rejected an argument from the Board of Patent Appeals and Interferences (the “Board”) that such evidence has no weight because it relates to use of the claimed composition, stating:

[T]he Board was mistaken to assert that the declarations only relate to the use of the claimed compositions. The declarations do more than that; they purport to show an unexpected result from use of the claimed composition, how the prior art taught away from the composition, and how a long-felt need existed for a new antivenom composition. While a statement of intended use may not render a known composition patentable, the claimed composition was not known, and whether it would have been obvious depends upon consideration of the rebuttal evidence.

Sullivan, at 498 F.3d 1353. The court in *Sullivan* cited with approval to *Papesch* and stated, “[t]he issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use.” *Sullivan* at 498 F.3d 1353.

In the instant application, assuming, *arguendo*, that the rejection based on *Hoeck et al.* and *Krezanoski* makes out a *prima facie* case of obviousness, it is clear that all rebuttal evidence must be given consideration, including evidence of teachings away (e.g., *Dobrozsi et al.*, *Ron et al.*) in the prior art when considered as a whole, evidence of unexpected properties of the claimed composition and evidence of addressing a long felt but unsolved need. This the Examiner has not done.

F. The objective evidence of nonobviousness, together with the other deficiencies in the prior art, discussed above, sufficiently rebuts any *prima facie* case of obviousness based on *Hoeck et al.* and *Krezanoski*.

This is not a situation where a claim is being made to a known composition based on discovery of a new use for that composition. It is clear that neither *Hoeck et al.* nor *Krezanoski* discloses the compositions of the rejected claims. It is also clear that neither *Hoeck et al.* nor *Krezanoski et al.* in any way suggests that N-acetylcysteine, in any formulation, has efficacy for treatment of N-acetylcysteine. Objective evidence of obviousness demonstrates that there was a long-felt but unsolved need for a treatment for oral mucositis in such patients and that the claimed composition addresses that need, and that the claimed composition contains a significant and unexpected property in relation to efficacy for treatment of such oral mucositis, and which property is not inherently present in the compositions of *Hoeck et al.* Moreover, the objective evidence demonstrates that the claimed composition can be significantly more effective for treating oral mucositis as a side effect of cancer radiation therapy than a comparison formulation of N-acetylcysteine in water, which comparison formulation directly corresponds to the solutions of N-acetylcysteine in water disclosed by *Hoeck et al.* for use in the “reservoir type” transdermal device and the solutions of N-acetylcysteine in the water subjected to in vitro testing in Examples 2 and 3 of *Hoeck et al.* See, *Hoeck et al.*, at column 3, lines 66-67; column 7, line 20 through column 8, line 44.

This objective evidence of nonobviousness, by itself, and in addition to the deficiencies in the prior art discussed above, effectively rebuts any case of nonobviousness based on *Hoeck et al.* and *Piechota*.

II. Ground 2, 35 U.S.C. § 103(a), *Hoeck et al.* in view of *Piechota*, Independent Claim 1.

A. The rejection of Ground 2 is similar to that of Ground 1, discussed above, and similar to the situation with Ground 1, claims subject to the rejection of Ground 2 are not obvious over *Hoeck et al.* and *Piechota* when the prior art is considered as a whole and because of objective evidence of nonobviousness.

Piechota et al. disclose a poloxamer-based drug delivery composition for topical application. The drug delivery composition of *Piechota* is very similar to the poloxamer-based drug delivery composition of *Krezanoski*, and the Examiner's reasoning in making the rejection for Ground 2 parallels the rejection made for Ground 1. The Examiner stated the same motivation for one of ordinary skill in the art to make the combination involving *Piechota* as stated for the combination involving *Krezanoski*, namely "the desire to increase drug absorption by the mucous membrane for rapid introduction into the system, as disclosed by the secondary reference[*Piechota*]." See, the Appealed Office Action at page 6. The Examiner may have repeated the same statement of motivation based on the similarities in the drug delivery compositions disclosed by *Piechota* and *Krezanoski*, but it is noted that there is no teaching by *Piechota* that the drug delivery composition of *Piechota* was found to increase drug absorption by the mucous membrane. However, as was the situation with *Krezanoski* with respect to the rejection of Ground 1, so also the claims rejected under Ground 2 are not obvious over *Hoeck et al.* and *Piechota* for at least the following reasons:

- 1) Considering the teachings of *Hoeck et al.* and *Piechota* in the context of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.* and *Piechota*; and
- 2) There is persuasive objective evidence of nonobviousness in relation to significant

and unexpected properties of the claimed composition as effective for treatment of oral mucositis as a side effect of cancer therapy and in relation to a long felt unsolved need addressed by the claimed composition for such a treatment, and which evidence the Examiner has inappropriately refused to give weight.

B. Based on a consideration of the prior art as a whole, one of ordinary skill in the art would not find obvious a combination of the teachings of *Hoeck et al.* and *Piechota* as suggested by the Examiner, similar to the discussion above for *Hoeck et al.* and *Krezanoski*.

The discussion above concerning the teachings of *Hoeck et al.* applies equally with respect to the rejection involving *Piechota*. In the extensive disclosure by *Hoeck et al.* concerning transdermal delivery of N-acetylcysteine for use as a mucolytic agent there is no indication that N-acetylcysteine in any compositional formulation would have efficacy for treatment of mucositis as a side effect of cancer therapy and there is no mention of poloxamer polymers, or poloxamer 407 specifically. Moreover, the drug delivery composition disclosed by *Piechota* is very similar to, and appears to be substantially a subset of the drug delivery composition disclosed by *Krezanoski*. Both *Piechota* and *Krezanoski* describe a reverse-thermal gelling drug delivery composition based on a poloxamer polymer in water, and both disclose a preference for the same poloxamer product, Pluronic® F127 (a poloxamer 407), and similar poloxamer concentration ranges, 10-26% (preferably 17-26%) for *Krezanoski* and 10-20% (preferably 12-17%) for *Piechota*. *Piechota* at column 3, lines 5-28 and column 4, lines 6-27; *Krezanoski* at column 5, lines 23-53.

Hoeck et al. provide significant guidance on transdermal delivery vehicles for transdermal delivery of N-acetylcysteine for use as a mucolytic agent, but do not disclose poloxamer-based drug delivery compositions. One of ordinary skill in the art considering delivery of N-acetylcysteine for use as a mucolytic agent would be guided by *Hoeck et al.* toward the compositions and devices for transdermal delivery disclosed by *Hoeck et al.* However, consistent with the discussion above concerning Ground 1, if one of ordinary skill in the art were

for some reason to look beyond *Hoeck et al.*, that person would encounter a multitude of other references on drug delivery compositions with different teachings, including, as discussed above, the teachings away by *Dobrozsi et al.* and *Ron et al.* from the reverse-thermal gelling drug delivery compositions of the types disclosed by *Piechota* and *Krezanoski*. Reference is again made to the Mathews Declaration for a further discussion of the teaching away by *Dobrozsi et al.* from compositions of the type disclosed by *Krezanoski* and *Piechota*.

Based on the guidance provided by *Hoeck et al.* concerning transdermal delivery and suitable delivery compositions and devices, the teaching away by *Hoeck et al.* of transmucosal delivery, teachings away in the prior art (e.g., *Dobrozsi et al.*, *Ron et al.*) from the use of drug delivery compositions of the type disclosed in *Piechota*, and a common sense recognition that there are a multitude of possibilities for drug delivery compositions, one of ordinary skill in the art would not find obvious a combination of N-acetylcysteine as a mucolytic agent or disclosed by *Hoeck et al.* with the drug delivery composition disclosed by *Piechota*.

C. The application specification and the Troha Declaration provide significant evidence of (a) an unexpected property of the claimed composition in relation to efficacy for treatment of oral mucositis as a side effect of cancer therapy and (b) a long felt but unsolved need for such a treatment that is addressed by the claimed composition, which evidence, together with the noted deficiencies in *Hoeck et al.* and *Piechota* discussed above, effectively rebuts any case of obviousness based on *Hoeck et al.* and *Piechota*.

Again, all rebuttal evidence of nonobviousness must be considered , including unexpected biological or pharmaceutical properties of a claimed composition. Evidence presented in the application specification and the Troha Declaration of an unexpected property of the claimed composition in relation to treatment of oral mucositis as a side effect of cancer therapy and of a long felt but unsolved need for such a treatment that is addressed by the claimed composition is discussed above, and that discussion applies equally to the rejection under Ground

2. As discussed above with Ground 1, the application specification and the Troha Declaration provide significant evidence of at least the following:

- (1) Poloxamer 407 formulated in water does not have efficacy for treatment of oral mucositis.
- (2) N-acetylcysteine has efficacy for treating oral mucositis;
- (3) The efficacy of oral mucositis treatment with N-acetylcysteine can be increased by a significant and surprising amount when formulated with the poloxamer 407 in a composition of the rejected claims relative to a formulation of N-acetylcysteine in water; and
- (4) Oral mucositis is a serious problem for certain cancer patients undergoing radiation therapy, there is a long-felt but unresolved need for a treatment of such oral mucositis, and the claimed composition can address that need.

D. Similar to Ground 1, with respect to the rejection of Ground 2 the Examiner erred in not giving any weight to the objective evidence of nonobviousness that the claimed composition has an unexpected property in relation to effectiveness for treatment of oral mucositis and as addressing a long felt but unresolved need for such treatment.

Again, in discussing the Troha Declaration on page 11 of the Appealed Office Action, the Examiner makes no mention of any consideration of the performance data presented and discussed in the Troha Declaration or in the application specification in relation to evidence of unexpected properties or evidence of addressing a long felt but unsolved need. However, on page 7 of the Appealed Office Action, in making the rejection based on *Hoeck et al.* and *Piechota*, the Examiner repeats the same above-quoted statement made in relation to the rejection of Ground 1, namely:

In regards to the intended use of the compositions of the combined reference [sic], intended use carries no weight in determining patentability because the compositions of

the combined references are substantially the same as those of the instant claims and therefore should be able to treat mucositis, because the compositions of the reference [sic] and the compositions of the instant claims are substantially the same.

Again, on page 10 of the Appealed Office Action, discussing the Troha Declaration in relation to prior claim rejections that were withdrawn, the Examiner states:

The Declaration is based on the intended use of the recited compositions and does not show a side-by-side comparison with the compositions of the cited references. This type of argument may have been considered effective if the claims were drawn to a method and not a composition . . . It [the Troha Declaration] does not show that the compositions of the references don't have the same capabilities or show unexpected results in view of the compositions of the references.

It is respectfully submitted that these cited statements, and the lack of consideration given to the Troha Declaration and the conclusions drawn from that declaration, are incorrect and not in conformance with controlling legal precedence, for the same reasons as discussed above with respect to Ground 1.

Assuming, *arguendo*, that the rejection based on *Hoeck et al.* and *Krezanoski* makes out a *prima facie* case of obviousness, it is clear that all rebuttal evidence must be given consideration, including evidence of unexpected properties of the claimed composition and evidence of addressing a long felt but unsolved need. This the Examiner has not done with respect to Ground 2 either.

E. The objective evidence of nonobviousness, alone and together with the deficiencies in the prior art, discussed above, effectively rebut any *prima facie* case of obviousness based on *Hoeck et al.* and *Piechota*.

Again, this is not a situation where a claim is being made to a known composition based on discovery of a new use for that composition. Neither *Hoeck et al.* nor *Piechota* discloses the claimed composition. Also, neither *Hoeck et al.* nor *Piechota* suggests that any formulation with N-acetylcysteine has a property of being efficacious for treatment of oral mucositis in cancer patients as a side effect of cancer radiation therapy. Objective evidence of obviousness demonstrates that there was a long felt but unsolved need for a treatment for oral mucositis in such patients and that the claimed composition addresses that need, and that the claimed composition contains a significant unexpected property in relation to efficacy for treatment of such oral mucositis, which property is not inherently present in compositions of *Hoeck et al.* for topical delivery of N-acetylcysteine as a mucolytic agent. This objective evidence of nonobviousness, by itself, and in addition to the deficiencies in the prior art discussed above, effectively rebuts by at least a preponderance of the evidence any case of nonobviousness based on *Hoeck et al.* and *Piechota*.

III. Additional Arguments Directed to Specific Dependent Claims.

A. Claims 15, 137, 140, 143, 146, 147

Each of these claims includes a limitation concerning the concentration of N-acetylcysteine, and each is argued separately, and these claims do not stand or fall together.

Claim 15, and Claims 137, 140, 143, 146 and 147 Generally

All of the pending claims require N-acetylcysteine in an amount effective as formulated in the composition to provide therapeutic effect for treatment of oral mucositis as a side effect of cancer therapy and Claim 15 further requires that in that context the concentration of the N-acetylcysteine is in a range of from about 0.001 weight percent to about 50 weight percent, and Claims 137, 140, 143, 146 and 147 have narrower requirements for the concentration of N-acetylcysteine. The Examiner's position on the concentration of N-acetylcysteine is that it would have been obvious for one ordinary skill in the art to have optimized the concentration of N-

acetylcysteine as a result effective variable, and the Examiner cites to the case of *In re Aller*, 220 F.2d 454, 105 USPQ 233 (CCPA 1955) for the proposition that such changes of result effective variables are not patentable where the difference is one of degree and not of kind. Appealed Office Action of pages 4 and 6. The situation here, however, with respect to the subject matter of the appealed claims in relation to the disclosures of *Hoeck et al.* is significantly different than the factual situation presented in *Aller*, and the reasoning behind the holding in *Aller* does not apply to this nonanalogous situation.

In *Aller*, the invention at issue was a process for making phenol, and the asserted prior art reference disclosed essentially the same process for making the same product (phenol), except that the invention used a somewhat lower temperature and higher concentration of one reactant, sulfuric acid. The subject matter (particular type of process) and the purpose of that subject matter (to make phenol) were the same in the invention and the prior art reference. Although the inventors in *Aller* asserted that the process of their invention resulted in higher yields of the phenol product, the Court noted that the improved results did not appear to be different in kind relative to the prior art and that logically the improvements can flow equally well from changes in degree resulting from routine variation of temperature and acid concentration, and that there was no showing of anything critical about parameters of the process of the invention.

The current situation is significantly different than the factual situation presented in *Aller*. The claims here are to a therapeutic composition that comprises N-acetylcysteine in a particular formulation with poloxamer 407 and a carrier liquid comprising water, with the N-acetylcysteine in an amount effective as formulated in the composition to provide therapeutic effect for treatment of mucositis as a side effect of cancer therapy, and dependent Claims 15, 137, 140, 143, 146 and 147 further require that the N-acetylcysteine be at a particular concentration or within a particular concentration range.

In contrast, *Hoeck et al.* is focused on transdermal administration of N-acetylcysteine to be effective to provide treatment as mucolytic agent. There is no disclosure in *Hoeck et al.* that N-acetylcysteine is a result effective variable for treatment of oral mucositis as a side effect of cancer therapy, and it could hardly be considered routine for one of ordinary skill in the art considering the teachings of *Hoeck et al.* to modify any composition to “optimize” the properties

of the composition for efficacy to treat oral mucositis as a side effect of cancer therapy. Moreover, even in the context of *Aller*, efficacy of the claimed composition for treatment of mucositis is indeed a difference of kind relative to efficacy of the transdermal vehicles of *Hoeck et al.* for treatment as a mucolytic agent.

The situation here is more analogous to that in the recent BPAI precedential decision of *Ex Parte Whalen*, Appeal 2007-4423, Application 10/281,142, decided July 23, 2008 (BPAI 2008). In *Whalen*, the Examiner had rejected a claim to a composition capable of embolizing an aneurysm at a vascular site and formulated with a biocompatible polymer of molecular weight sufficient to impart to the composition a certain high viscosity. Prior art compositions were characterized as comprising similar components used in overlapping concentration ranges and the Examiner asserted that it was prima facie obvious for one of ordinary skill in the art to optimize the viscosity range of the prior art compositions by routine experimentation to arrive at the claimed composition. The BPAI rejected the Examiner's position because there was no teaching in the cited reference or explanation based on scientific reasoning that would support a conclusion that those skilled in the art would have considered it obvious to 'optimize' the viscosity to a higher value as claimed by applicant, where the prior art references suggested that low viscosity was a desired property of such concentrations. Here, the only disclosure concerning N-acetylcysteine in the *Hoeck et al.*, *Krezanoski* and *Piechota* is for treatment as a mucolytic agent as disclosed in *Hoeck et al.* Based on that disclosure, there is no basis for finding a motivation by one of ordinary skill in the art to "optimize" any composition for efficacy of treatment in the quite different context of oral mucositis as a side effect of cancer therapy.

To the extent that Claims 137, 140, 143, 146 and 147 have narrower requirements for the concentration of N-acetylcysteine stated in Claim 15, the position with respect to each those claims that one of ordinary skill in the art would find the features obvious as an "optimization" is even more tenuous and those claims are further argued separately below.

Claim 137

Claim 137 further requires that the N-acetylcysteine comprises from 0.1 to 20 weight percent of the composition. There is no motivation in any of *Hoeck et al.*, *Krezanoski* or

Piechota to make the claimed composition with a property of being effective for treatment of oral mucositis as a side effect of cancer therapy, including the recited poloxamer 407 and N-acetylcysteine, and with the recited concentration of N-acetylcysteine.

Claim 140

Claim 140 further requires that the N-acetylcysteine comprises about 10 weight percent of the composition. There is no motivation in any of *Hoeck et al.*, *Krezanoski* or *Piechota* to make the claimed composition, with a property of being effective for treatment of oral mucositis as a side effect of cancer therapy, including the recited poloxamer 407 and N-acetylcysteine, and with the concentration of N-acetylcysteine recited in Claim 140. Also, 10 weight percent N-acetylcysteine corresponds with a concentration of N-acetylcysteine in clinical trials, discussed above.

Claim 143

Claim 143 is dependent under Claim 142, and requires that the composition is adapted for delivery to a patient when the therapeutic composition is at a refrigerated temperature, in a range from 1°C to 10°C, at which the composition is in the form of a flowable medium with the N-acetylcysteine and poloxamer 407 dissolved in the water, and that the composition comprises from 0.1 weight percent to 25 weight percent of the composition. There is no motivation in any of *Hoeck et al.*, *Krezanoski* or *Piechota* to make the claimed composition, with a property of being effective for treatment of oral mucositis as a side effect of cancer therapy, including the recited poloxamer 407 and N-acetylcysteine, and with the recited concentration of N-acetylcysteine. Moreover, although both *Krezanoski* and *Piechota* disclose drug delivery compositions made using poloxamer polymers, including poloxamer 407, having reverse-thermal viscosity, one of ordinary skill in the art would have no motivation for making such a composition containing N-acetylcysteine, let alone also with the specific properties at the refrigerated temperature.

Claim 145

Claim 145 depends under Claim 143, and further requires that the N-acetylcysteine comprises 10 weight percent to 20 weight percent of the composition. In addition to the arguments regarding Claim 143, there is no motivation in any of *Hoeck et al.*, *Krezanoski* or *Piechota* to make the claimed composition of Claim 145 with the narrower compositional requirements for N-acetylcysteine.

Claim 146

Claim 146 also depends under Claim 143, and further requires that the N-acetylcysteine comprises from 0.1 up to 10 weight percent of the composition. In addition to the arguments regarding Claim 143, there is no motivation in any of *Hoeck et al.*, *Krezanoski* or *Piechota* to make the claimed composition of Claim 146 with the narrower compositional requirements for N-acetylcysteine.

Claim 147

Claim 147 also depends under Claim 143, and further requires that the N-acetylcysteine comprises about 10 weight percent of the composition. In addition to the arguments regarding Claim 143, there is no motivation in any of *Hoeck et al.*, *Krezanoski* or *Piechota* to make the claimed composition of Claim 145 with the narrower compositional requirement for N-acetylcysteine. Also, 10 weight percent N-acetylcysteine corresponds with a concentration of N-acetylcysteine in clinical trials, discussed above.

B. Claim 20.

Claim 20 further requires that the composition be formulated with water in an amount that does not interact with the poloxamer 407 to impart reverse-thermal gelation properties to the composition. As discussed in the specification, reverse-thermal gelation is a subset of reverse-thermal viscosity behavior. See, the specification at page 11, lines 15-29. Under claim 20, the composition is required to have reverse-thermal viscosity behavior, but not exhibit reverse thermal gelation. Both *Krezanoski* and *Piechota* disclose reverse-thermal gelation, but not

reverse-thermal viscosity behavior without reverse-thermal gelation in relation to their compositions. *See, Krezanoski* at column 2, lines 49-62; column 3, line 67 through column 4. *See, Piechota* at column 2, lines 18-3 and 52-59. Moreover, it does not appear as though the Appealed Office Action even addresses the subject matter of this claim.

C. Claim 25.

Claim 25 depends under Claim 24, and requires that the composition has a property that both of the poloxamer 407 and the N-acetylcysteine are dissolved in the water of the carrier liquid when the composition is at a temperature of 5°C. None of *Hoeck et al.*, *Krezanoski* and *Piechota* discloses or suggests a composition having these properties when the composition is at 5°C. Moreover, it does not appear as though the Appealed Office Action even addresses the subject matter of this claim.

D. Claim 31.

Claim 31 further requires that the composition comprises a bioadhesive agent that is different than the N-acetylcysteine and the poloxamer 407. None of *Hoeck et al.*, *Krezanoski* and *Piechota* discloses or suggests such a composition also having such a bioadhesive agent. Moreover, it does not appear as though the Appealed Office Action even addresses the subject matter of this claim.

E. Claims 133, 134 and 135.

Each of these Claims further requires that the composition have a property of particular viscosity behavior when the temperature of the composition is raised from a temperature of 1°C to 37°C, with Claim 133 requiring that the composition exhibits an increase in viscosity from no larger than about 60cP to at least about 70cP, with Claim 134 requiring that the composition exhibits an increase in viscosity from no larger than about 60cP to at least about 80cP, and with

Claim 135 requiring that the composition exhibits an increase in viscosity from no larger than about 50cP to at least about 70cP. On pages 4 and 6 of the Appealed Office Action, the Examiner takes the position, with respect to viscosity, that the compositions of *Krezanoski* and *Piechota* use overlapping amounts of poloxamer and water with those of the claims, and therefore those compositions should have substantially the same viscosity profile as the claimed compositions. The Examiner's position, therefore, appears to be that viscosity requirements of Claims 133, 134 and 135 are inherent in the compositions of *Krezanoski* and *Piechota*, and therefore also are obvious in the composition of the claims. However, such a position is not consistent with the law concerning inherency.

As discussed in the BPAI decision in *Whalen*, cited above, a finding of inherency cannot be based on a probability or possibility of a property, and that the burden to disprove inherency shifts to an applicant only after the examiner makes a satisfactory showing based on evidence or scientific reasoning that the property is inherent in the prior art. *Whalen* at p. 13. In the instant case, *Krezanoski* recognizes that the viscosity of its reverse-thermal gelling compositions including a poloxamer polymer are affected by the particular solutes included in the composition. For example, *Krezanoski* states, at column 5, lines 32-42:

The concentration of the polyoxyethylene-polyoxypropylene condensate is an important parameter. Significantly, by ready adjustment of the concentration of the copolymer to accommodate other solutes present in the vehicle, any desired gel transition temperature in the critical range of above ambient temperature and below body temperature can be achieved. Thus, the principal consideration is the selection of a concentration which in conjunction with all of the constituents of the vehicle composition, will provide a sol-gel transition temperature in the required range.

Krezanoski also discloses that a variety of different solutes may be included in a composition, such as for example salts to adjust osmotic pressure, preservatives and germicides, surfactants, and different pharmaceutically active materials. See, *Krezanoski* at column 6, line 7 through column 7, line 52. *Piechota* also discloses a number of different possible ingredients for

inclusion in the delivery composition. See, *Piechota* at column 5, lines 5-35. Recognizing based on the teachings of *Krezanoski* that the viscosity of the delivery compositions of the types disclosed in *Krezanoski* and *Piechota* will vary depending upon the particular composition and solutes included, the viscosity limitations of Claims 133, 134 and 135 are not inherently disclosed by the references, and especially because the claimed composition necessarily includes N-acetylcysteine, a component not disclosed by either *Krezanoski* or *Piechota*. Moreover, there is no disclosure in any of *Hoeck et al.*, *Krezanoski* or *Piechota* that would motivate one of ordinary skill in the art to prepare the compositions of any of Claims 133, 134 or 135.

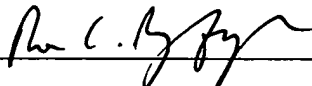
CONCLUSION

The rejections stated in the Appealed Office Action are unsupportable, and it is respectfully requested that the rejections be reversed, and the application proceed to issuance.

Respectfully submitted,

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APPENDIX A
CLAIMS INVOLVED IN APPEAL

1. A therapeutic composition useful for treatment of oral mucositis as a side effect of cancer therapy, the composition comprising:

N-acetylcysteine in an amount effective as formulated in the composition to provide therapeutic effect for treatment of the mucositis;

from 5 weight percent to 20 weight percent poloxamer 407;

a carrier liquid comprising water in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart reverse-thermal viscosity behavior to the therapeutic composition, wherein the composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C;

wherein, at some temperature in a range of from 2°C to 8°C the therapeutic composition is in the form of an aqueous solution with the poloxamer 407 and the N-acetylcysteine dissolved in the water.

15. The therapeutic composition of Claim 1, wherein the N-acetylcysteine comprises from about 0.001 percent by weight to about 50 percent by weight of the composition.

17. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C to 20°C.

19. The therapeutic composition of Claim 1, wherein the biocompatible polymer, as formulated in the therapeutic composition, imparts a reverse-thermal gelation property to the composition with the composition having a reverse-thermal liquid-gel transition temperature within a range of from 1°C to 37°C, so that the therapeutic composition gels as the temperature of the therapeutic composition is increased from below to above the reverse-thermal gel transition temperature.

20. The therapeutic composition of Claim 1, wherein the amount of the water, as formulated in the composition, does not interact with the poloxamer 407 to impart reverse-thermal gelation properties to the composition.

24. The therapeutic composition of Claim 1, wherein the poloxamer 407 is dissolved in the water when the composition is at a temperature of 5°C.

25. The therapeutic composition of Claim 24, wherein the N-acetylcysteine is dissolved in the water when the composition is at a temperature of 5°C.

31. The therapeutic composition of Claim 1, comprising a bioadhesive agent that is different than the N-acetylcysteine and the poloxamer 407.

35. The therapeutic composition of Claim 1, comprising at least one taste masking component.

38. The therapeutic composition of Claim 1, comprising at least one preservative component.

133. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 60cP to at least about 70cP when a temperature of the composition is increased from 1°C to 37°C.

134. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 60cP to at least about 80cP when a temperature of the composition is increased from 1°C to 37°C.

135. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 50cP to at least about 70cP when a temperature of the composition is increased from 1°C to 37°C.

136. The therapeutic composition of Claim 1, wherein the composition comprises reverse-thermal gelation properties with a reverse-thermal liquid-gel transition temperature within the range of temperatures.

137. The therapeutic composition of Claim 1, wherein the therapeutic composition comprises from 0.1 to 20 weight percent of the N-acetylcysteine.

140. The method of Claim 137, wherein the therapeutic composition comprises about 10 weight percent of the N-acetylcysteine.

142. The therapeutic composition of Claim 1, wherein:
the therapeutic composition is adapted for delivery to a patient when the therapeutic composition is at a refrigerated temperature in a range of from 1°C to 10°C; and

when the therapeutic composition is at the refrigerated temperature, it is in the form of a flowable medium with each of the N-acetylcysteine and the poloxamer 407 dissolved in the water.

143. The therapeutic composition of Claim 142, comprising from 0.1 weight percent to 25 weight percent of the N-acetylcysteine.

145. The therapeutic composition of Claim 143, comprising from 10 weight percent to 20 weight percent of the poloxamer 407.

146. The therapeutic composition of Claim 143, comprising up to 10 weight percent of the N-acetylcysteine.

147. The therapeutic composition of Claim 143, comprising about 10 weight percent of the N-acetylcysteine.

148. The therapeutic composition of Claim 147, comprising from 10 weight percent to 20 weight percent of the poloxamer 407.

149. The therapeutic composition of Claim 143, wherein when the therapeutic composition is at a temperature of 2°C the therapeutic composition has sufficient fluidity for use as a mouthwash that can be swished in the oral cavity.

150. The therapeutic composition of Claim 143, wherein when the therapeutic composition is at a temperature of 2°C the viscosity of the therapeutic composition is no larger than 60 cP.

151. The therapeutic composition of Claim 143, wherein the carrier liquid is water.

152. The therapeutic composition of Claim 143, wherein the carrier liquid comprises, in addition to the water, at least one component selected from the group consisting of ethanol and a polyol.

**APPENDIX B
EVIDENCE**

U.S. Patent Documents:

1. 6,620,428 by *Hoeck et al.* (“**Hoeck et al.**”)
2. 4,188,373 by *Krezanoski* (“**Krezanoski**”)
3. 5,256,396 by *Piechota, Jr.* (“**Piechota.**”)
4. 6,503,955 by Dobrozsi et al. (“**Dobrozsi et al.**”)
5. 6316,011 by Ron et al. (“**Ron et al.**”)

Foreign Patent Documents:

Non-Patent Technical Papers:

Other Evidence:

Rule 132 Declaration of Janice M. Troha, including Exhibits (“**Troha Declaration**”)

Rule 132 Declaration of Anthony James Mathews, including Appendices (“**Mathews Declaration**”)



US006620428B1

(12) **United States Patent**
Hoeck et al.

(10) **Patent No.: US 6,620,428 B1**
(45) **Date of Patent: Sep. 16, 2003**

(54) **TRANSDERMALLY ADMINISTERED
ACETYL-CYSTEINE AS MUCOLYTIC AGENT**

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(73) Assignee: **Pharmacia AB**, Stockholm (SE)

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§ 371 (c)(1),

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PCT Pub. Date: **Oct. 30, 1997**

(30) **Foreign Application Priority Data**

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(51) Int. Cl.⁷ **A61K 9/70; A61L 15/16;
A61F 13/00; A61N 1/30**

(52) U.S. Cl. **424/449; 424/447; 424/448**

(58) Field of Search **424/447, 448,
424/449; 604/20**

(56) **References Cited**

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EP	0481294	4/1992
WO	95 00136	1/1995
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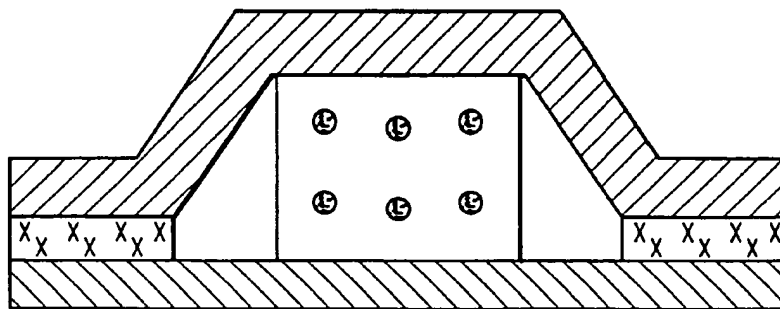
Primary Examiner—Shelley A. Dodson

(74) *Attorney, Agent, or Firm*—Birch, Stewart, Kölasch & Birch, LLP

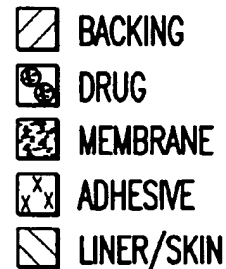
(57) **ABSTRACT**

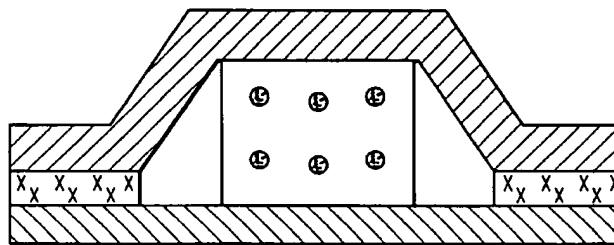
Device for transdermal administration of N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, optionally together with pharmaceutically acceptable carrier(s) to a human being or an animal in order to achieve a mucolytic effect. Use of a mucolytic compound comprising N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, optionally together with pharmaceutically acceptable carrier(s), for the manufacture of a composition for achieving a mucolytic effect in a human being or an animal. Method for achieving a mucolytic effect in a living body by transdermal administration of a compound comprising N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, optionally together with pharmaceutically acceptable carrier(s).

10 Claims, 4 Drawing Sheets

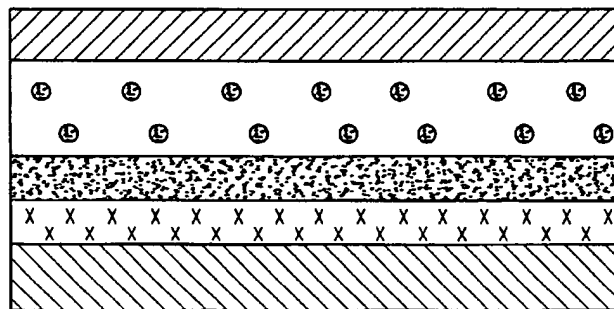
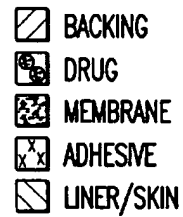


MATRIX

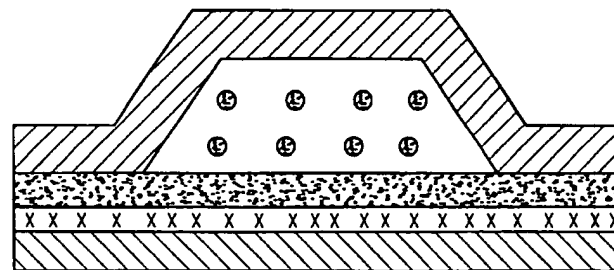
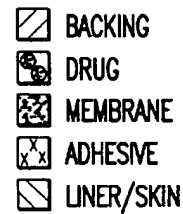




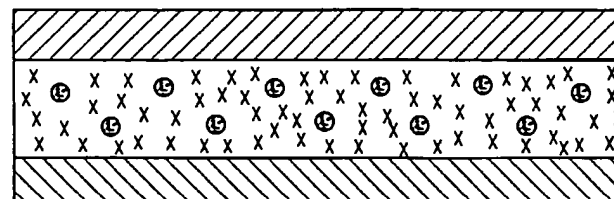
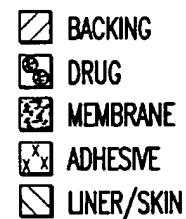
MATRIX
FIG. 1A



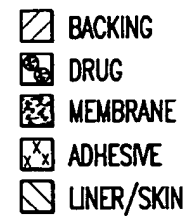
MULTI-LAMINATE
FIG. 1B



RESERVOIR
FIG. 1C



DRUG-IN-ADHESIVE
FIG. 1D



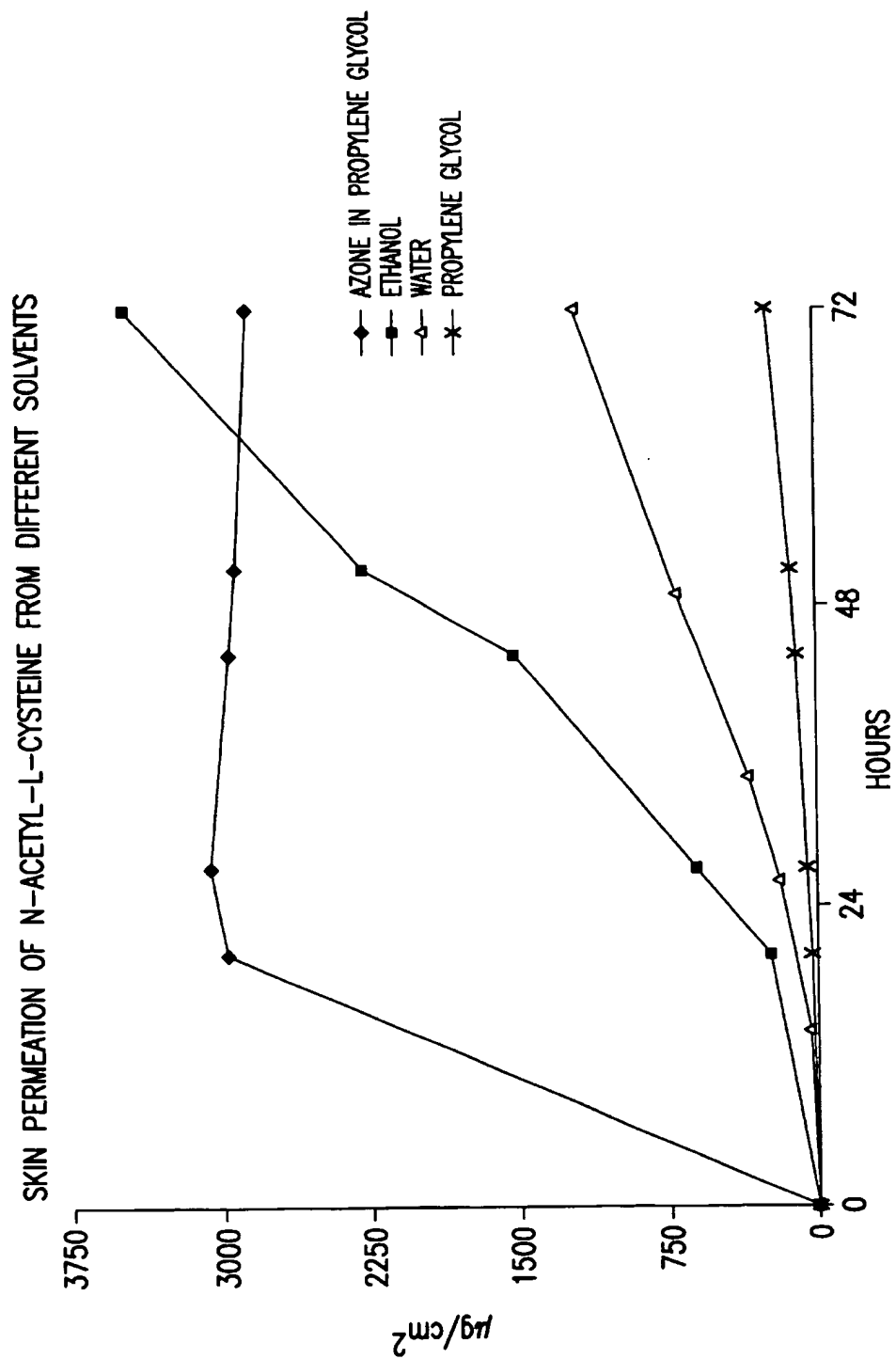


FIG.2

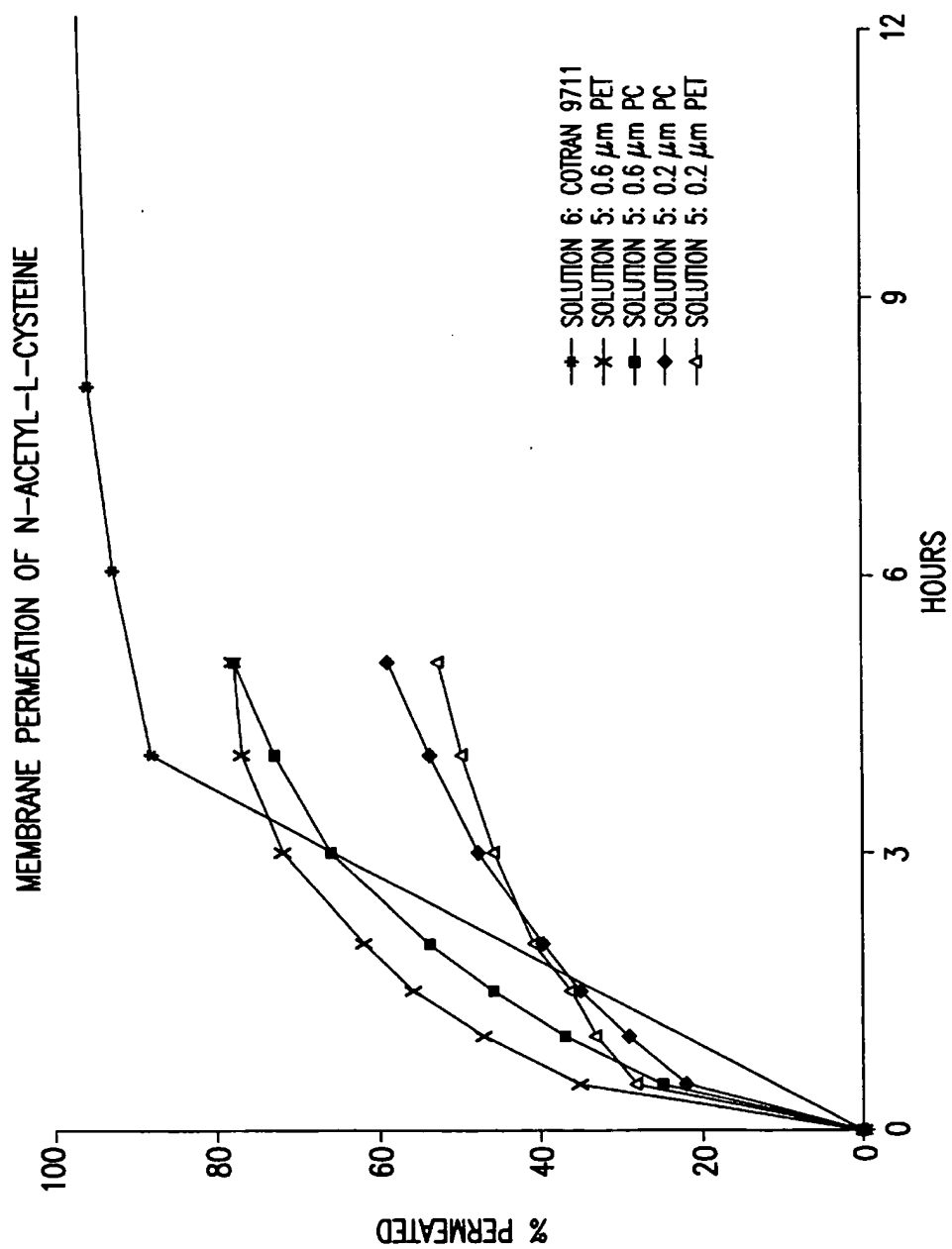


FIG.3

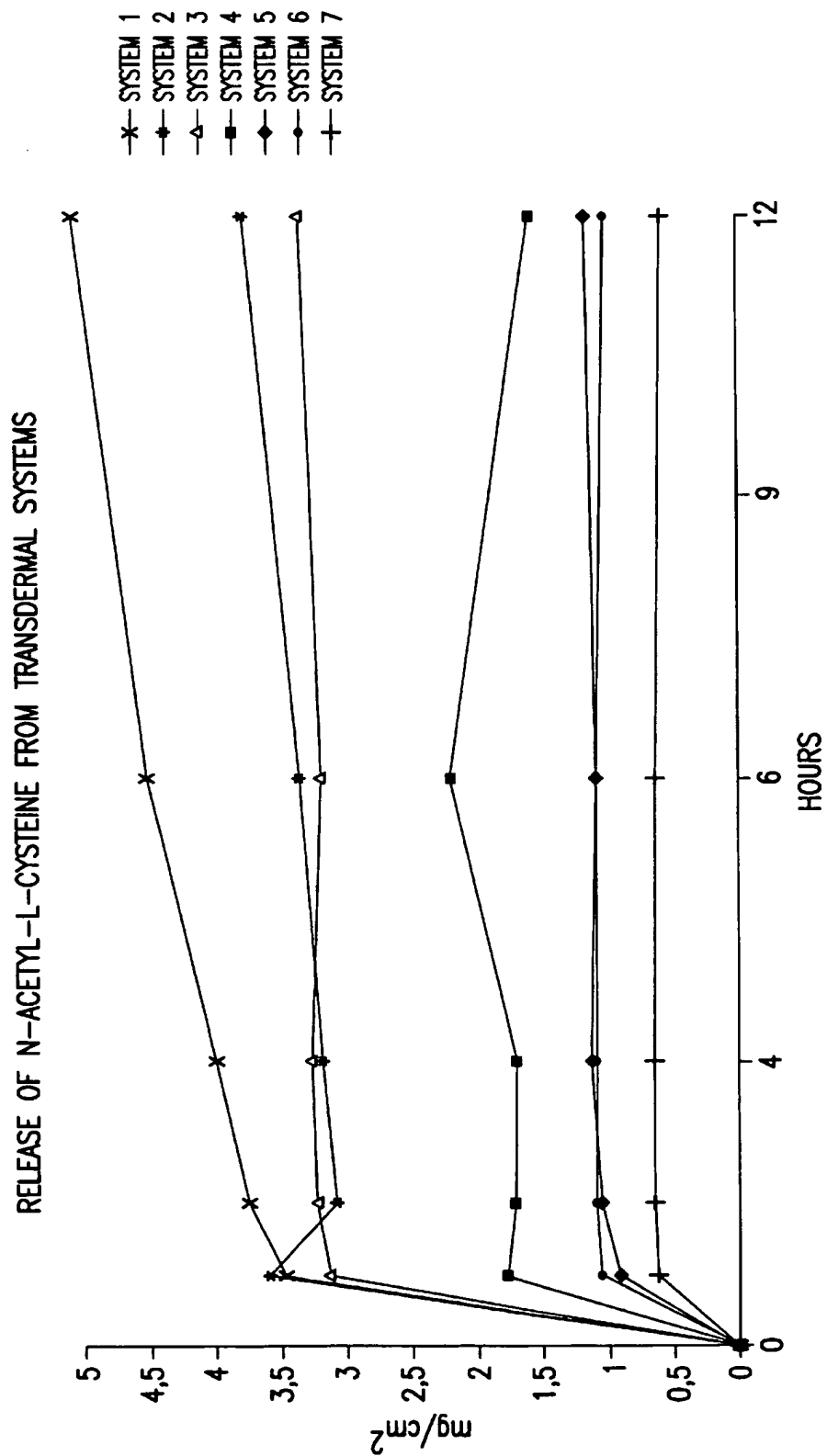


FIG.4

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TRANSDERMALLY ADMINISTERED ACETYL-CYSTEINE AS MUCOLYTIC AGENT

This application is the national phase under 35 U.S.C. §371 of prior PCT International Application No. PCT/SE97/00483 which has an International filing date of Mar. 21, 1997 which designated the United States of America, the entire contents of which are hereby incorporated by reference.

This invention relates to use of N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, for the manufacturing of a medicament to be administered transdermally for achieving a mucolytic effect and to methods of treating diseases being treatable with a mucolytic agent by transdermal administration of N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof.

BACKGROUND

N-Acetyl-L-cysteine, $C_5H_9NO_3S$, is an expectorant. Its synthesis was disclosed in Smith et al., *J. Org. Chem.*, 1961;26:820. N-Acetyl-L-cysteine decreases the viscosity of mucous and purulent expectorate. The mucolytic effect after peroral administration in connection with bronchitis is though not well-documented. However, several investigations have proved effect just below the significance limit. Anyhow, the patients' wellbeing during treatment with N-Acetyl-L-cysteine is significant. N-Acetyl-L-cysteine is registered as a mucolytic agent for peroral administration under trade marks such as Fabrol®, Inspir® and Mucosmust®.

N-Acetyl-L-cysteine has a low bioavailability, only about 4–10%, when administered perorally, see Mack R. Holdiness, "Clinical Pharmacokinetics of N-Acetylcysteine", *Clin. Pharmacokinet.*, 1991;20(2):123–134. The following references confirm the low bioavailability of N-Acetyl-L-cysteine: L. Borgström et al., "Pharmacokinetics of N-Acetylcysteine in Man", *Eur J Clin Pharmacol.* 1986;31:217–222, L. Borgström et al., "Dose dependent pharmacokinetics of N-Acetylcysteine after oral dosing to man", *Biopharmaceutics & Drug Disposition*, 1990(II):131–136, B. Olsson et al., "Pharmacokinetics and Bioavailability of Reduced and Oxidized N-Acetylcysteine", *Eur J Clin Pharmacol.* 1988;34:77–82. Martindale, "The Extra Pharmacopoeia", London, 1993, recommends a peroral dosing of 200 mg three times daily to adults, 200 mg once daily for children up to 2 years and 200 mg twice daily for children aged 2 to 6 years.

Deutsche Apotheker Zeitung; 34; 1990 indicates that the maximum plasma level is reached 2 to 3 hours after oral administration. The same reference indicates 4% bioavailability upon oral administration.

Currently the mucolytic effect is achieved by inhalation or peroral administration of N-Acetyl-L-cysteine. The inhalation route can only be used for temporary relief and several dosings per day are necessary. Administration of N-Acetyl-L-cysteine through the oral route is hampered by a low bioavailability of the drug due to an extensive first-pass metabolism and side effects such as nausea and skin disorders, like rash.

The above disadvantages are removed or reduced upon administering N-Acetyl-L-cysteine transdermally.

N-Acetyl-L-cysteine is a fairly unstable drug in aqueous formulation. This could be improved by incorporation into a lipophilic medium like the one used in pressure sensitive adhesives, such as polyisobutylenes, acrylates and silicone derivatives.

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PRIOR ART

Transdermal administration of N-Acetyl-L-cysteine is known from a few patents, e.g. from WO 95/00136 (ARNDT ET AL.) for treating hyperkeratosis, and WO 93/07903 (DECKNER ET AL.) wherein is disclosed certain cationic polymers which may improve transdermal penetration of a number of drugs, such as N-Acetyl-L-cysteine. Anyhow there is no patent which discloses transdermal administration of N-Acetyl-L-cysteine for achieving a mucolytic effect.

EP 0481294 (SPIRIG AG) discloses oral administration of acetylcysteine, but does not mention transdermal administration thereof.

Only sparse studies on skin permeation of N-Acetyl-L-cysteine have been reported in the literature with the aim to use N-Acetyl-L-cysteine as a model substance in connection with experiments to compare skin permeability between different animal species such as rat, rabbit, pig, monkey and man, see Methodius J. Bartek et al., "Skin permeability in vivo in rat, rabbit, pig and man", 32nd Annual Meeting of the Society for Investigative Dermatology Inc., Boston, Mass., 1971, June 18–20, and Ronald C. Wester et al., *Clin. Pharmacokinet.*, 1992;23(4):253–266. From inter alia the above Bartek reference it is evident that the transdermal penetration of N-Acetyl-L-cysteine hitherto was considered to be very low.

There is no literature reference which discloses transdermal administration of N-Acetyl-L-cysteine for achieving a mucolytic effect.

Hence the present invention being transdermally administered N-Acetyl-L-cysteine as mucolytic agent, as further described below, is both new and inventive over prior art.

OBJECTS OF THE INVENTION

The above mentioned disadvantages and side effects are removed or reduced when N-Acetyl-L-cysteine is administered transdermally.

Accordingly, a first object of the present invention is to provide a device for transdermal administration of N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, for achieving a mucolytic effect. The administration can be to a human being or to an animal. The mucolytic effect is for treating any kind of mucous and purulent expectorates, such as, but not exclusively, mucous and purulent expectorates occurring in association with upper and lower respiratory infections, including chronic bronchitis and asthma, and with cystic fibrosis, emphysema, tracheostomy and post-operative pulmonary complications. The pharmacological effect is primarily achieved by reduction of the viscosity for the mucous and purulent expectorates.

A second object of the invention is to provide use of a mucolytic compound comprising N-Acetyl-L-cysteine for the manufacture of a composition to be administered transdermally for treating mucous and purulent expectorates, primarily by decreasing their viscosity, or conditions associated with mucous and purulent expectorates.

A third object of the invention is to provide a method of treating diseases, in humans or animals, which are treatable with mucolytic agents by administering N-Acetyl-L-cysteine transdermally.

Other objects of the invention will become apparent to one skilled in the art, and still other objects will become apparent hereinafter.

SUMMARY OF THE INVENTION

The present invention relates to transdermal administration of N-Acetyl-L-cysteine, optionally encompassing salts,

prodrugs and metabolites thereof for achieving a mucolytic effect. This effect is primarily achieved through the systemic effect of N-Acetyl-L-cysteine whereby in the first place the viscosity of mucous and purulent expectorates is decreased. Anyhow, other mechanisms of actions are not excluded.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A–1D are schematic drawings of different types of devices for transdermal delivery of drugs.

FIG. 2 is a diagram showing in vitro skin permeation of N-Acetyl-L-cysteine from different solvents according to Example 2.

FIG. 3 is a diagram showing in vitro permeation of N-Acetyl-L-cysteine through different membranes in accordance with Example 3.

FIG. 4 is a diagram showing in vitro release of N-Acetyl-L-cysteine from different transdermal systems in accordance with Examples 4 and 5.

DETAILED DESCRIPTION OF THE INVENTION

Transdermal delivery of drugs can be accomplished from topical products such as ointments or cremes or from transdermal devices. The present invention relates to administration via transdermal devices, which usually are called transdermal patches.

Devices usable as transdermal patches can be categorized in many different ways. A comprehensive categorization of transdermal devices is found in Steven Wick, "Developing A Drug-In-Adhesive Design For Transdermal Drug Delivery", *Adhesives Age*, 1995; 38(10):18–24, which hereby is incorporated by reference. Wick essentially divides transdermal devices into the below four main groups:

- the reservoir type, in which the drug is placed in a liquid or a gel and is delivered to the skin across a rate-moderating membrane;
- the matrix type, in which the drug is placed within a non-adhesive polymeric material, typically a hydrogel or soft polymer;
- the drug-in-adhesive type, in which the drug is placed within an adhesive polymer;
- the multi-laminate type, which is similar to the drug-in-adhesive design, but which incorporates an additional layer of pressure sensitive adhesive to cover the entire device and affix it to the skin.

The above four main types of transdermal devices are schematically illustrated in FIGS. 1A–1D.

A fifth important type, not mentioned by Wick, is the iontophoretic type, in which an electrical potential gradient is used for transferring the drug through the skin—see further e.g. Parminder Singh et al, "Iontophoresis in Drug Delivery: Basic Principles and Applications", *Critical Reviews in Therapeutic Drug Carrier Systems*, 1994; 11 (2&3):161–213.

The above split-up into groups is not very strict as variations and combinations of each may be envisaged. So may a multi-laminate type device encompass a device with many layers in a sandwich construction, such as the drug in one layer, excipients such as enhancers in a further layer, a membrane in another layer and an adhesive in still another layer. Or it could be composed of several drug-in-adhesive layers or combinations of the above layers.

The liquid or gel used in the above reservoir type device could be hydrophilic or lipophilic, such as water, alcohols,

mineral oils, silicone fluids, various copolymers, such as ethylene vinyl acetate, vinyl acetate or polyvinyl alcohol/polyvinyl pyrrolidone. The reservoir may also include dyes, inert fillers, diluents, antioxidants, penetration enhancers, stabilizers, solubilizing agents and other pharmacologically inactive pharmaceutical agents being well known in the art.

The adhesives used are generally of three types, being the rubber type, encompassing inter alia polyisobutylenes, the acrylate type and the silicone type. The adhesives may be chemically modified and may have a wide range of molecular weights. To the adhesive could be added several types of excipients such as fillers, stabilizers, plasticizers, buffering agents, penetration enhancers, penetration retarders, solubilizing agents and other pharmaceutical ingredients being well known in the art.

Polymer films which may be used for making the rate-moderating membrane include, without limitation, those comprising low density polyethylene, high density polyethylene, ethyl vinyl acetate copolymers and other suitable polymers.

The backing layer serves the purposes of preventing passage of the drug or environmental moisture through the surface of the patch distant from the skin, and also for providing support for the system, where needed. The backing layer may be chosen so that the end product is appealing to the users, whether children, adults, elderly people or other customer groups. The backing layer is impermeable to the passage of N-Acetyl-L-cysteine or inactive ingredients being present in the formulation and can be flexible or nonflexible. Suitable materials include, without limitation, polyester, polyethylene terephthalate, some types of nylon, polypropylene, metallized polyester films, polyvinylidene chloride and aluminium foil.

The release liner can be made of the same materials as the backing layer.

As will be clear further below the invention according to the present application encompasses administration of N-Acetyl-L-cysteine via all hitherto known types of devices for transdermal administration. Mainly the above categorization will be adhered to in this application. Anyhow, this does not exclude that transdermal devices which might fit better according to some other categorization also are included in the present invention.

It is well known in the art that the properties of the skin as such influence the penetration of the drug through the skin into the systemic circulation. It could thus be said that the skin controls the drug penetration rate. Anyhow, as the skin as such is no part of the present invention the behaviour of the skin in connection with transdermal administration will not be discussed in detail. It is also well accepted in the art that when rate controlling properties are attributed to a transdermal device is meant properties associated with the release rate from the device as such. It is also evident that when a transdermal device is designed to exhibit a certain release performance the properties of the skin need be taken into consideration during the design process.

The rate control ability is often a very important feature for a transdermal device in order to deliver the correct drug amount to the patient at the correct time. Thereby maximum efficacy is achieved while side effects are minimized. Many factors influence the rate control ability of a transdermal device. In the below Table 1 the most important such factors are listed and their influence in the respective device type is marked. A plus sign indicates that the influence is strong. The absence of a plus sign does not exclude that the corresponding factor has at least some influence.

TABLE 1

Factor	TYPE OF DEVICE			
	Reservoir	Matrix	Drug-in-adhesive	Multi-laminate
-Polymer type(s)	+	+	+	+
-Modification of the polymer(s)		+	+	+
-Activity, i.e. concentration, of drug, e.g. supersaturation	+	+	+	+
-Additives in polymer(s)				
Enhancer(s)	+	+	+	+
Cyclo-dextrine(s)	+	+	+	+
Retarder(s)	+	+	+	+
-pH-adjustment	+	+	+	+
-Solubilizer(s)	+	+	+	+
-Emulsifier(s)	+	+	+	+
-Membrane(s)	+			
Hydrophilic	+			
Lipophilic	+			
Thickness	+			
Pore Size	+			
Density	+			
-Chemical stabilizer(s)	+	+	+	+

As a comparably high loading of N-Acetyl-L-cysteine is needed for achieving the desirable therapeutic effect the reservoir type device and the multilaminate type device, including several drug-containing layers, are presently considered to be the best modes for making the present transdermal delivery of N-Acetyl-L-cysteine.

It is also desirable to include, at least in some device types, one or more transdermal penetration enhancing substance(s) in order to increase the amount of N-Acetyl-L-cysteine that may penetrate the skin and that eventually may reach the systemic circulation. Enhancers suitable in the present invention may be categorized in the below groups, although enhancers not belonging to any of these groups are not excluded.

alcohols, such as short chain alcohols, e.g. ethanol and the like, long chain fatty alcohols, e.g. lauryl alcohols, and the like, and polyalcohols, e.g. propylene glycol, glycerin and the like;

amides, such as amides with long aliphatic chains, or aromatic amides like N,N-diethyl-m-toluamide;

amino acids;

azone and azone-like compounds;

essential oils, i.e. essential oils or constituents thereof, such as 1-carvone, 1-menthone and the like;

fatty acids and fatty acid esters, such as oleic acid, lauric acid and the like, further esters of fatty acids, such as isopropyl myristate, and various esters of lauric acid and of oleic acid and the like;

macrocylic compounds, such as cyclopentadecanone and cyclodextrins;

phospholipid and phosphate compounds, such as phospholipids;

2-pyrrolidone compounds; and

miscellaneous compounds, like sulfoxides, such as dimethyl sulfoxides, and fatty acid ethers, such as Laureth-9 and polyoxylaurylether.

Combinations of enhancers from different groups in the above categorization may prove to be very useful and efficient.

For overviews of enhancers, see further e.g. G.C. Santus et al., "Transdermal enhancer patent literature", Journal of Controlled Release, 1993;25:1-20 and Eric W. Smith et al., "percutaneous penetration enhancers", CRC Press Inc., 1995.

DETAILED DESCRIPTION OF THE INVENTION

The following examples are intended to illustrate but not to limit the scope of the invention, although the embodiments named are of particular interest for our intended purposes.

MATERIALS AND APPARATUS USED IN THE EXAMPLES

Materials

N-Acetyl-L-cysteine, Fluka
Sodium hydroxide, Merck
Propylene glycol, Merck
Azone, Discovery Therapeutics Inc.
Ethanol 99.9%, De Danske Spritfabrikker
Hydrochloric acid, Merck
Polycarbonate membrane 0.2 μm in pore diameter, Whatman
Polycarbonate membrane 0.6 μm in pore diameter, Whatman
Polyester membrane 0.2 μm in pore diameter, Whatman
Polyester membrane 0.6 μm in pore diameter, Whatman Cotran 9711, 3M
Polyester film S 2016, Rexam Release
Polyester film Scotchpak 1220, 3M
Polyester film Scotchpak 1109, 3M
Eudragit RL 30 D, Röhm GmbH Chemische Fabrik
Eudragit NE 30 D, Röhm GmbH Chemische Fabrik
Plastoid E35H, Röhm GmbH Chemische Fabrik
Polyvidone 90, BASF
Span 20, Sorbitanmonolaurate, Maximex
MA-24 Medical Grade Adhesive, Adhesives Research Inc.
ETA-2 Medical Grade Adhesive, Adhesives Research Inc.
Durotak 387-2287, National Starch and Chemical B.V.
Triethyl citrate, Fluka
Sodium bisulfite, Sigma

Apparatus

Franz diffusion cells
Coating equipment: RP Print Coat Instrument LTD., Type KCC 202 Control Coater System with vacuum bed and rods (100 and 400 μm)
UV-spectrophotometer
Drug Release Apparatus 5, paddle over disk, described in USP 23, p. 1797
HPLC-device: LKB 2150 pump
LKB 2141 variable wavelength monitor
LKB 2221 integrator
Marathon-XT autosampler (20 μl injected) connected to a Multi Temperature 111 cooling bath adjusted to 4° C.
Analytical column, 25 cm \times 4.0 mm i.d., packed with Lichrosorb RP18, 5 μm .

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The column was eluted isocratically at ambient temperature with a mobile phase consisting of water-acetonitrile (970:50 v/v) adjusted with diluted phosphoric acid to a pH=3. The flow rate was 1.0 ml/min. and the column effluent was monitored at 220 nm.

Example 1

Analysis of the receptor solutions described in Examples 2 and 3, and of the stability samples described in Example 6.

Quantitative determination of N-Acetyl-L-cysteine in the receptor solution samples from the skin permeation studies in Example 2 and from the membrane permeation studies in Example 3, and quantitative determination of N-Acetyl-L-cysteine in the samples from the stability studies in Example 6, was done by the HPLC method described under Apparatus.

Example 2

In vitro skin permeation studies from solutions of N-Acetyl-L-cysteine.

Solution 1

500 mg N-Acetyl-L-cysteine was dissolved in 5 ml demineralized water.

The pH of the solution was adjusted to 5 by the addition of sodium hydroxide.

Solution 2

250 mg N-Acetyl-L-cysteine was dissolved in 5 ml propylene glycol.

Solution 3

250 mg N-Acetyl-L-cysteine was dissolved in 5 ml propylene glycol containing 50 mg/ml of azone.

Solution 4

500 mg N-Acetyl-L-cysteine was dissolved in 5 ml ethanol.

In vitro permeation of N-Acetyl-L-cysteine from the solutions 1, 2, 3 and 4 through dermatomed pig skin was investigated in Franz diffusion Cells.

Skin pieces with a thickness of approximately 765 μm were dermatomed from full thickness pig skin and mounted in glass diffusion cells with an available diffusion area of 1.8 cm^2 . Pig skin is a fully accepted model for human skin. The solutions 1, 2, 3 and 4 were applied separately on the skin surfaces and the dermal sides were all exposed to 12.1 ml receptor solution consisting of 0.0001M hydrochloric acid equilibrated to $37\pm 1^\circ\text{C}$.

Permeation of N-Acetyl-L-cysteine was followed by removing samples periodically and measuring the concentration by the HPLC method according to Example 1. The cumulative amount of N-Acetyl-L-cysteine appearing in the receptor solution versus time is shown in FIG. 2. An increase in the permeated amount of N-Acetyl-L-cysteine is seen in the following order: Propylene glycol, water, ethanol and propylene glycol containing 5% azone added used as solvents. The estimated fluxes of N-Acetyl-L-cysteine are in the range from approximately 4 to 48 $\mu\text{g}/\text{cm}^2/\text{h}$ for the above solvents without enhancer added. The results show that it is possible to optimize the flux of N-Acetyl-L-cysteine through the skin by using an appropriate solvent. A surprisingly high

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rate of permeation was observed for the solution with added azone as about 3000 $\mu\text{g}/\text{cm}^2$ was permeated after 20 hours.

Example 3

In vitro permeation studies across artificial membranes from solutions of N-Acetyl-L-cysteine, imitating the reservoir type transdermal device.

Solution 5

50 mg N-Acetyl-L-cysteine was dissolved in 5 ml demineralized water.

Solution 6

50 mg N-Acetyl-L-cysteine was dissolved in 5 ml ethanol.

In vitro permeation of N-Acetyl-L-cysteine from the solutions 5 and 6 across 5 different types of artificial membranes was investigated in Franz diffusion cells.

Artificial membranes of the following types were studied: Whatman 0.2 μm PC (polycarbonate), Whatman 0.6 μm PC (polycarbonate), Whatman 0.2 μm PET (polyester), Whatman 0.6 μm PET (polyester) and Cotran 9711 (microporous polyethylene film). The membranes were mounted in glass diffusion cells with an available diffusion area of 1.8 cm^2 . Solution 5 was applied on the surfaces on all the above Whatman membranes while solution 6 only was applied on Cotran 9711. The opposite sides of the membranes were all exposed to 12.1 ml receptor solution consisting of 0.0001M hydrochloric acid equilibrated to $37\pm 1^\circ\text{C}$. Permeation of N-Acetyl-L-cysteine was followed by removing samples periodically and measuring the concentration by the HPLC method according to Example 1. The cumulative amount of N-Acetyl-L-cysteine appearing in the receptor solution versus time is shown in FIG. 3. An increase in the permeated amount of N-Acetyl-L-cysteine is seen in the following order of used membranes: Whatman 0.2 μm PET, Whatman 0.2 μm PC, Whatman 0.6 μm PC, Whatman 0.6 μm PET and Cotran 9711.

The results show that it is possible to control the release rate of N-Acetyl-L-cysteine from a reservoir type device by the choice of solvent and of membrane.

Example 4

Transdermal drug delivery systems with N-Acetyl-L-cysteine as the active substance.

System 1 (Drug-in-adhesive Type, Acrylate)

2.5 g N-Acetyl-L-cysteine and 350 mg Span 20 were dispersed in 10 g ETA-2 Medical Grade Adhesive to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μm). After drying at 80°C . for 10 minutes, a polyester film, Scotchpak 1220, was laminated onto the dried drug gel. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 4 mg/cm^2 .

System 2 (Drug-in-adhesive Type, Acrylate)

2.5 g N-Acetyl-L-cysteine and 350 mg Span 20 were dispersed in 10 g Durotak 387-2287 to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μm). After drying at 80°C . for 10 minutes, a polyester film, Scotchpak 1220, was laminated onto the dried drug gel. The

resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 4 mg/cm².

System 3 (Drug-in-adhesive Type, Polyisobutylene)

5 g N-Acetyl-L-cysteine and 700 mg Span 20 were dispersed in 20 g MA-24 Medical Grade Adhesive to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μ m). After drying at 80° C. for 10 minutes, a polyester film, Scotchpak 1220, was laminated onto the dried drug gel. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 3 mg/cm².

System 4 (Multi-laminate Type, Waterbased Acrylate)

4 g N-Acetyl-L-cysteine was dispersed in a mixture of 12.8 g Eudragit RL 30 D, 12.8 g PVP gel (20% Polyvidone 90 swelled in water) and 4 g propylene glycol to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μ m). After drying at 80° C. for 10 minutes, an adhesive layer consisting of Plastoid E35H (wet layer=100 μ m) coated on a polyester film, S 2016, was laminated onto the dried drug gel. The polyester film, S 2016, in contact with the drug gel was removed, and Scotchpak 1220 was laminated onto the drug gel as backing. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 1.5 mg/cm².

System 5 (Multi-laminate Type, Waterbased Acrylate)

4 g N-Acetyl-L-cysteine was dispersed in a mixture of 12.8 g Eudragit RL 30 D, 12.8 g PVP gel (20% Polyvidone 90 swelled in water), 4 g propylene glycol and 200 mg 1M sodium hydroxide solution to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μ m). After drying at 25° C. for 2 hours, an adhesive layer consisting of Plastoid E35H (wet layer=100 μ m) coated on a polyester film, S 2016, was laminated onto the dried drug gel. The polyester film, S 2016, in contact with the drug gel was removed, and Scotchpak 1109 was laminated onto the drug gel as backing. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 1.5 mg/cm².

System 6 (Multi-laminate Type, Waterbased Acrylate)

2.4 g N-Acetyl-L-cysteine was dispersed in a mixture of 3 g Eudragit NE 30 D and 45 g Plastoid E35H to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μ m). After drying at 80° C. for 10 minutes, an adhesive layer consisting of Plastoid E35H (wet layer=100 μ m) coated on a polyester film, S 2016, was laminated onto the dried drug gel. The polyester film, S 2016, in contact with the drug gel was removed and Scotchpak 1109 was laminated onto the drug gel as backing. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 1 mg/cm².

System 7 (Drug-in-adhesive Type, Waterbased Acrylate)

2.4 g N-Acetyl-L-cysteine was dispersed in a mixture of 3 g Eudragit NE 30 D and 45 g Plastoid E35H to give the drug gel. The drug gel was solvent cast onto a polyester film, S 2016, by means of the coating equipment (wet layer=400 μ m). After drying at 80° C. for 10 minutes, a polyester film, Scotchpak 1109, was laminated onto the dried drug gel. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 1 mg/cm².

System 8 (Multi-laminate Type, Waterbased Acrylate)

4 g N-Acetyl-L-cysteine was dispersed in a mixture of 25 g Eudragit RL 30 D, 1.9 g triethyl citrate, 200 mg 1M sodium hydroxide solution and 20 mg sodium bisulfite to give the drug gel. The drug gel was solvent cast onto a polyester film, S2016, by means of the coating equipment (wet layer=400 mm). After drying at 25° C. for 2 hours an adhesive layer consisting of Plastoid E35H (wet layer=100 mm) coated on a polyester film, S2016, was laminated onto the dried drug gel. The polyester film, S2016, in contact with the drug gel was removed, and Scotchpak 1109 was laminated onto the drug gel as backing. The resulting sheet was die-cut into patches which were kept at room temperature until use. The concentration of N-Acetyl-L-cysteine in the patches was approximately 1 mg/cm².

In vitro release studies according to Example 5 were carried out on the systems 1, 2, 3, 4, 5, 6 and 7 described above. The results of these studies are shown graphically in FIG. 4.

The results show that different release profiles can be achieved from different types of devices.

Example 5

In vitro release studies of the transdermal drug delivery systems 1, 2, 3, 4, 5, 6 and 7 according to Example 4.

The apparatus used was Apparatus 5, paddle over disk, described under Apparatus above. Patches of 7.1 cm² were applied to the disk assembly, using a suitable adhesive, with the release surface facing up. The dissolution medium used was 600 ml of 0.0001M hydrochloric acid equilibrated to 32±0.5° C. Samples were withdrawn at 1, 2, 4, 8 and 16 hours, respectively. The amount of N-Acetyl-L-cysteine in the samples was determined either by UV-spectrophotometry at 215 nm (Systems 1, 2 and 3) or by the HPLC method described under Apparatus (Systems 4, 5, 6 and 7) and the concentration of the respective systems was expressed in mg N-Acetyl-L-cysteine per cm².

Example 6

Stability studies were carried out on drug delivery Systems 5 and 8 according to the above Example 4. Patches from these Systems 5 and 8 were stored at room temperature and quantitative determination of N-Acetyl-L-cysteine was done by the HPLC method described under Apparatus after 0, 4 and 12 weeks of storage respectively. The results of these studies are shown in Table 2 below.

TABLE 2

STABILITY OF N-ACETYL-L-CYSTEINE IN PATCHES		
Storage time (weeks)	Concentration of N-Acetyl-L-cysteine (%)	
	System 5	System 8
0	100	100
4	81	97
12	54	90

The above results show that it is possible to improve the stability of N-Acetyl-L-cysteine in a patch formulation, e.g. by adding a stabilizer such as sodium bisulfite.

A reservoir type device may be manufactured by heat sealing a membrane such as described in Example 3 to a backing containing the drug in a suitable vehicle.

An iontophoretic type device may be manufactured essentially according to embodiments disclosed in e.g. Parminder Singh et al., "Iontophoresis in Drug Delivery: Basic Principles and Applications", Critical Reviews in Therapeutic Drug Carrier Systems, 1994; 11 (2&3):161-213. The administration of N-Acetyl-L-cysteine is not disclosed in this reference. Anyhow it lies within the present invention to modify, using the disclosure in the present application, the embodiments according to said reference to become suitable for the administration of N-Acetyl-L-cysteine.

The above examples show that it is possible to administer N-Acetyl-L-cysteine and to control its release rate using all known types of devices for transdermal drug administration.

Transdermal administration of N-Acetyl-L-cysteine can be improved by use of the prodrug concept. N-Acetyl-L-cysteine is by nature hydrophilic and it is known that hydrophilic drugs may permeate the skin to a limited extent due to an unfavourable partition coefficient between lipids and water. The hydrophilicity of N-Acetyl-L-cysteine could be reduced by chemical modification of the carboxylic group and/or the thiol group. Several pro-drugs of N-Acetyl-L-cysteine are described in Anne H. Kahns et al., "Prodrugs as drug delivery systems. 107. Synthesis and chemical and enzymatic hydrolysis kinetics of various mono- and diester-prodrugs of N-Acetyl-L-cysteine" are disclosed in Internat. J. Pharma, 1990;62:193-205, but only with the aim of reducing the metabolism of N-Acetyl-L-cysteine in the liver or in the intestine; the authors do not discuss the utility of such pro-drugs for transdermal administration. Pro-drugs of N-Acetyl-L-cysteine may also possess improved characteristics in patch formulations with respect to degradation of N-Acetyl-L-cysteine or to decreased possible skin metabolism.

It is evident that the above mentioned Examples may be modified to encompass also metabolites and prodrugs of N-Acetyl-L-cysteine.

The stability of N-Acetyl-L-cysteine can be improved by the addition of stabilizers, which may prevent degradation of N-Acetyl-L-cysteine. The stabilizers could be disodium edetate, ascorbic acid, sodium bisulfite, sodium hypophosphite, L-cystin, L-cysteine or other suitable stabilizing compounds. Adjustment of the protolytic balance, i.e. pH in aqueous systems, may also increase the stability of patch formulations.

A neglectable degradation of N-Acetyl-L-cysteine, less than 1%, may produce compounds with an unpleasant smell. This smell could be masked by the addition of fragrances or flavouring agents, such as peppermint oil, menthol etc.

As the period of time from the first application of a transdermal device according to the present invention until a therapeutically effective serum level of N-Acetyl-L-cysteine is achieved is in the order 2-3 hours the complementary and concomitant use of another administration form may be of value. Oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal, administration of N-Acetyl-L-cysteine results in that the drug reaches the system more rapidly than through the transdermal route. As mentioned above said non-transdermal administration forms have the disadvantage of a lower bioavailability than the transdermal form of administration. Anyhow this disadvantage, and problems related thereto, may be temporarily tolerated if a mucolytic effect is desirable in the period of time before the therapeutic effect is achieved from the transdermal device.

One suitable use of the mentioned forms of administration is to administer N-Acetyl-L-cysteine through the oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal, route at approximately the same time as the first transdermal device is applied. Thereafter new transdermal devices are applied to ensure the correct plasma level without further administration through the oral, sublingual, buccal, nasal, pulmonary and rectal, or possibly other transmucosal, routes. The above concomitant use of different administration forms is especially useful in certain situations, such as, but not exclusively, some time prior to oral presentations, attendance to conferences and visits to theatres, concerts and church. It is thus feasible to market set of formulations including devices for transdermal administration as well as devices or formulations for oral, sublingual, buccal, nasal, rectal, pulmonary and rectal, and possibly other transmucosal, administration of N-Acetyl-L-cysteine.

Another envisageable concomitant use according to the present invention is to apply a second transdermal device while a priorly applied first transdermal device is still adhered to the patient's skin while still delivering some amount of the drug. The utility behind this use is as follows. Suppose that the transdermal devices used deliver the drug during 36 hours. The first evening one such device is applied. The following evening the device still delivers the drug, though usually with a lower flux rate than earlier. If now this second evening a second transdermal device is applied while the first one is left on the skin the fluxes from the first and second device will add to a useful flux as the flux from the first device successively decreases while the drug from the second device only reaches the systemic circulation after some hours. By using transdermal devices in this way a more stable therapeutically effective plasma level of the drug during an extended period of time is achieved than if for example are used devices delivering for 24 hours and being replaced every 24 hours of course also other useful combinations of concomitantly used transdermal devices are envisageable.

As it might be advantageous that the mucolytic effect during certain periods should be allowed to be minor it might be desirable not to treat mucous and purulent expectorates during too long continuous periods of time. It is within the present invention to administer N-Acetyl-L-cysteine in such a way that a therapeutically effective systemic level of N-Acetyl-L-cysteine prevails mainly during those periods of time during day and night when a mucolytic effect is more desirable, and, consequently, in such a way that a less than therapeutically effective systemic level of N-Acetyl-L-cysteine prevails mainly during those periods of time during day and night when a mucolytic effect

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is less desirable. The above object is achievable by applying the transdermal device at the appropriate time during day or night in combination with designing the device with the appropriate release profile.

Dosage

Assuming that the oral bioavailability is around 5%, that the transdermal bioavailability is around 100% and that the usual peroral dose is 200–600 mg/day then the transdermal dose is equivalent to 10–30 mg/day. This daily transdermal dose corresponds to a flux rate of 15–45 $\mu\text{g}/\text{cm}^2/\text{hour}$ from a transdermal device with an area of 30 cm^2 under the assumption that no metabolism takes place in the skin and that the device delivers the drug during 24 hours.

The area of a transdermal device being convenient for a patient to wear is in the range from 5 to 50 cm^2 . The corresponding patch loading should be at least from about 0.3 mg/cm^2 to about 1.0 mg/cm^2 for a transdermal device with an area of 30 cm^2 . As the drug content of a transdermal device is never completely depleted during its application to a patient a higher loading than above must be anticipated, preferably from about 0.5 mg/cm^2 to about 3.0 mg/cm^2 . The above indicated loadings in mg/cm^2 are to be considered as average loadings for an average size device. It is known that the driving force for the release of a drug from a transdermal device is related to the drug concentration, i.e. number of mg of drug/ cm^3 . Therefore the above indicated loadings in mg/cm^2 are to be adjusted according to the actual areal size and thickness of the device in order to arrive at the desirable therapeutic effect.

Loadings for different sizes and types of devices for transdermal administration, taking into account different age groups and types of patients, range from about 0.1 mg/cm^2 to about 10 mg/cm^2 of N-Acetyl-L-cysteine. The hourly flux rate of dextromethorphan ranges from about 1 $\mu\text{g}/\text{cm}^2/\text{hour}$ to about 100 $\mu\text{g}/\text{cm}^2/\text{hour}$. The effective transdermally delivered amount of N-Acetyl-L-cysteine is from about 0.05 mg/kg bodyweight to about 5 mg/kg bodyweight.

It should also be contemplated that a device for transdermal delivery during 8–12 hours would be clinically more relevant than a device for delivery during 24 hours. Such a device with limited release duration may be used for periods when the problems arising from mucous and purulent expectorates are most embarrassing.

The mentioned device may either be taken off from the skin after 8–12 hours in order to stop further delivery, or be designed in such a way that its delivery drops to negligible or non-pharmacological levels after 8–12 hours. In this latter case the device may remain on the skin after 8–12 hours without the patient risking further delivery thereafter which facilitates the patient's handling of the device. Such devices are known per se, see eg U.S. Pat. No. 4,915,950 (MIRANDA ET AL.)—although not for delivery of N-Acetyl-L-cysteine.

When N-Acetyl-L-cysteine is administered in a transdermal device the latter should preferably be occlusive, which means that the device does not permit water to migrate outwardly from the patient. Thereby the hydration of the

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skin is increased which favors the penetration of N-Acetyl-L-cysteine through the skin.

What is claimed is:

1. A method for achieving a mucolytic effect in a living body by decreasing the viscosity of mucous and purulent expectorates, said method comprising

transdermally administering a compound comprising N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), wherein transdermal administration is achieved by a transdermal device comprising one or more layers selected from the group consisting of a membrane or an adhesive polymer.

2. The method of claim 1, wherein the mucolytic effect is achieved through systemic effect of the transdermally administered compound.

3. The method of claim 1, or 2, wherein the mucolytic effect is achieved through decreasing the viscosity of mucous and purulent expectorates.

4. The method of claim 1, wherein the transdermal administration is carried out using a device for transdermal delivery, such device is selected from the group consisting of reservoir, matrix, drug-in-adhesive, multi-laminate, iontophoretic and combinations thereof.

5. The method of claim 1, wherein more than one device for transdermal delivery is used at a time.

6. The method of claim 1, wherein the effective amount of N-Acetyl-L-cysteine is from about 0.05 mg/kg bodyweight to about 5 mg/kg bodyweight during a predefined period of time.

7. A method for achieving a mucolytic effect in a living body by decreasing the viscosity of mucous and purulent expectorates, which comprises

transdermally administering a compound comprising N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s) in combination with oral, sublingual, buccal, nasal, pulmonary, rectal and/or trans-mucosal administration of a compound comprising N-Acetyl-L-cysteine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

8. The method of claim 1, wherein the N-Acetyl-L-cysteine is administered in such a way that a therapeutically effective systemic level of N-Acetyl-L-cysteine prevails mainly during those periods of time during day and night when a mucolytic effect is most desirable.

9. The method of claim 1, wherein the N-Acetyl-L-cysteine is administered in such a way that a less than therapeutically effective systemic level of N-Acetyl-L-cysteine prevails mainly during those periods of time during day and night when a mucolytic effect is less desirable.

10. The method of claim 6, wherein the predefined period of time is 8, 12 or 24 hours.

* * * * *

[54] CLEAR, WATER-MISCIBLE, LIQUID PHARMACEUTICAL VEHICLES AND COMPOSITIONS WHICH GEL AT BODY TEMPERATURE FOR DRUG DELIVERY TO MUCOUS MEMBRANES

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[*] Notice: The portion of the term of this patent subsequent to Jul. 11, 1995, has been disclaimed.

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Related U.S. Application Data

[63] Continuation of Ser. No. 661,612, Feb. 26, 1976, Pat. No. 4,100,271.

[51] Int. Cl.² A61K 31/74

[52] U.S. Cl. 424/78; 424/177; 424/181; 424/228; 424/243; 424/250; 424/273 R; 424/324; 424/330

[58] Field of Search 424/78

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[57] ABSTRACT

Pharmaceutical vehicles for delivery of pharmacologically active chemical materials to mucous membranes, as well as pharmaceutically active compositions containing such vehicles, are provided. The pharmaceutical vehicles are clear, water-miscible, physiologically-acceptable, liquid compositions which gel to a thickened, non-flowing and adhering consistency at human body temperature. They are liquid at ambient room temperature and have a gel transition temperature in the range of from about 25° C. to about 40° C. Aqueous solutions of certain polyoxyethylene-polyoxypropylene condensates are suitable vehicles. Also provided are pharmaceutical compositions containing added pharmacologically active chemical material, i.e., a drug or medicament. A method of delivering the drug or medicament to a mucous membrane is also provided.

4 Claims, No Drawings

CLEAR, WATER-MISCIBLE, LIQUID PHARMACEUTICAL VEHICLES AND COMPOSITIONS WHICH GEL AT BODY TEMPERATURE FOR DRUG DELIVERY TO MUCOUS MEMBRANES

This is a continuation of application Ser. No. 661,612, filed Feb. 26, 1976, now U.S. Pat. No. 4,100,271.

This invention relates to a new pharmaceutical vehicle for carrying a pharmaceutically active material, i.e., a drug or medicament, and delivering it to mucous membranes. More specifically, the present invention is directed to a clear, liquid, water-miscible pharmaceutical vehicle which thickens to a gel at human body temperatures. In other aspects, the present invention relates to a pharmaceutical composition useful for therapeutic or protective application to mucous membranes comprising a pharmacologically effective amount of a drug or medicament dissolved in said pharmaceutical vehicle and to a method of delivering a drug or medicament to a mucous membrane by applying the pharmaceutical composition to the site to be treated.

BACKGROUND OF THE INVENTION

There are many drugs known to be useful for treatment of afflictions or protection of mucous membranes, e.g., for ocular diseases. A practical problem in connection with therapeutic or protective application of pharmaceutically active chemicals to afflicted mucous membranes resides in the delivery of the chemical or drug to the affected area in need of treatment. Various formulations and techniques have been attempted to deliver medicaments to mucous membranes, but there is a need for improved pharmaceutical vehicles for delivery of drugs, and it is this need to which the present invention is addressed.

For example, drugs have been formulated into aqueous solutions. However, the fleeting presence and poor contact of aqueous solutions applied to mucous membranes has been a disadvantage. The only adequate application of medication in solution form to mucous membranes is usually accomplished by employing continuous lavage or interrupted irrigation. This approach is often wasteful of expensive drugs and poses a major problem of inconvenience. Thus, treatment of severe keratoconjunctivitis sicca with isotonic salt solutions requires ocular instillation every 15-30 minutes.

The use of viscous aqueous solutions is usually more convenient. For example, the aforementioned isotonic salt solutions can often be applied every 1-2 hours and accomplish the same therapeutic objective if the solution is made viscous. Drugs have been formulated into aqueous suspensions made viscous by the addition of gums or cellulose-modified synthetic derivatives or incorporated into oleaginous vehicles or bases consisting of natural plant or animal fats or modifications thereof or petroleum-derived hydrocarbons.

Indeed, aqueous vehicles which are thickened by the addition of selected gums or cellulose-derived viscosity building agents are perhaps the most commonly used media for delivery of drugs or medicaments to mucous membranes. Generally, the viscosity of such preparation ranges from about 25 cps to indeterminate values in stiff gels. Nearly uniform drug delivery is possible with such vehicles, and they frequently provide desirable protection to the mucous membranes.

In contrast, non-viscous aqueous suspensions have many disadvantages and are not typically used. A major problem is rapid settling of the suspended drug. This gives rise to undesirable need for continuous stirring during administration in order to deliver a uniform dose.

While thick gels would seem to offer the best potential in terms of protection as well as holding and delivering medication, they in fact have some disadvantages. In some instances, they are difficult to apply from their respective commercial containers. Moreover, thick gels do not spread readily over the area being treated, and possibly painful spreading and rubbing may be necessary. Also, on evaporation of the water from the vehicle, a cosmetically unappealing hard granular or flaky residue often results at the site of the application.

Attempts to use oily vehicles to increase drug delivery and prolong ensuing pharmacologic action have not met with uniform success. The use of oleaginous vehicles, whether anhydrous or in emulsion form (oil-in-water or water-in-oil), may have advantages for certain therapeutic indications, if the vehicle will adhere. However, since normal mucous membranes are always moist with aqueous tissue fluids, and water does not mix readily with oil bases, application, uniform spreading, and retention all become difficult. Perhaps the only time oily or emulsion vehicles are used successfully is when the mucous tissue is abnormally dry because of disease.

Another approach to the delivery of drugs or medicaments to mucous membranes is the recent development of silicone plastic devices which deliver drugs at predetermined, nearly uniform, zero order rates extending from a few days to several years. However, the usefulness of such devices depends upon a constant supply of tissue fluid or glandular secretion; in the absence of fluid, plastic devices are not operative. Such devices are not designed to offer any protection to an inflamed mucous membrane. Discomfort often associated with the devices, and inadvertent loss of the devices, are additional problems.

The existence of all these disparate approaches to drug delivery to mucous membranes evidences the need for new pharmaceutical vehicles. Against the background of this array of formulations and devices with all their attendant problems, the present invention fills that need.

SUMMARY OF THE INVENTION

In its broadest sense, the present invention provides a pharmaceutical vehicle useful for delivering a compatible, pharmacologically active chemical, i.e., drug or medicament, to a mucous membrane which consists of a clear, water-miscible, physiologically-acceptable, liquid composition which gels to a thickened, non-flowing and adhering consistency at human body temperature. Pharmaceutical vehicles in accordance with the invention are liquid at ambient room temperatures below about 30° C., preferably about 25° C. and below. They have a sol-gel transition temperature in the range of from about 25° C. to about 40° C., preferably from about 25° C. to about 35° C., and most preferably from about 29° C. to about 31° C.

In accordance with the present invention, it has been discovered that aqueous solutions of certain polyoxyethylene-polyoxypropylene block copolymers are useful pharmaceutical vehicles having the properties set forth above. In particular, the present invention provides a pharmaceutical vehicle or base for carrying a pharma-

ceutically active material, i.e., a drug or medicament, which comprises:

- (a) from about 10% to about 26%, preferably from about 17% to about 26%, by weight of a polyoxyethylene-polyoxypropylene block copolymer in which the number of polyoxyethylene units is at least about 50%, preferably about 70%, of the total number of monomeric units in the total molecule, the block copolymer having an average molecular weight of from about 7500 to about 15,500, preferably about 11,500, a room temperature solubility in water of greater than about 10 grams per 100 ml. of water, and a cloud point in 1% aqueous solution of at least about 100° C.; and
- (b) from about 74% to about 90% by weight water, the vehicle having a sol-gel or gel transition temperature in the range of from about 25° C. to about 40° C., preferably from about 25° C. to about 35° C., and especially from about 29° C. to about 31° C.

The pharmaceutical vehicle may also include various additives, such as auxiliary non-ionic surfactants, salts to adjust osmotic pressure, buffer systems to control pH, and preservatives. Preferably, the vehicle contains at least one water-soluble compatible salt for adjustment of osmotic pressure in sufficient amount to provide a solution salt content equivalent to from about 0.1% to about 10.0%, especially from about 0.5% to about 6.0%, sodium chloride. It is also preferred that the vehicle contain a compatible preservative or germicide in an amount effective to afford protection to the vehicle against bacterial contamination.

In accordance with this invention, the pharmaceutical vehicle preferably has a pH in the range of 3.5 to 9.5. Particularly preferred is a pH in the range of from about 6.0 to about 8.5, and especially from about 6.2 to about 7.8.

In keeping with the concept of the present invention, there is also provided a pharmaceutical composition useful for protective or therapeutic application to mucous membranes comprising a solution of a pharmacologically effective amount of a pharmaceutically active material, i.e., drug or medicament, in a pharmaceutical vehicle as described above. The concept of this invention is not dependent on the nature of the drug, and any compatible pharmaceutically active material may be used. Preferably, the drug is water-soluble. However, drugs which are not ordinarily soluble in water may also be employed, and where needed, auxiliary nonionic surfactants, which are typically well tolerated by mucous membranes, can be added to increase the solvent action, while maintaining the vehicle gel transition temperature within the required range.

It has been discovered that a wide variety of useful pharmaceuticals which are not ordinarily soluble in water and are presently marketed only in suspension form can in fact be dissolved in the polyoxyethylene-polyoxypropylene vehicles of the present invention. In some instances, the addition of auxiliary nonionic surfactants was found necessary. However, the critical gel transition temperature is maintained.

An important aspect of this invention is that the pharmaceutical vehicles and compositions are liquid at ambient room temperatures and can be applied to the affected mucous membrane area by conventional liquid depositing means, including dispensation to the area of treatment from standard plastic squeeze bottles or in drop form. At body temperatures above 30° C., the vehicle or base passes through the sol-gel transition

temperature and gels to a thickened, non-flowing and adhering consistency, holding and delivering the medication as required and for prolonged periods of time.

Thus, in accordance with the present invention, there is also provided a method of delivering a drug or medicament to a mucous membrane comprising the steps of providing a pharmaceutical composition which comprises a solution of the pharmaceutically active material in the pharmaceutical vehicle; and applying the pharmaceutical composition to the mucous membranes. The composition is applied to the mucous membrane in an amount sufficient to deliver a non-toxic, pharmacologically effective amount of the drug to the intended site of treatment.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the invention, the pharmaceutical vehicle consists of a clear, water-miscible, physiologically-acceptable medium which is liquid at ambient temperature below about 30° C. and thickens to a gel at body temperatures above about 30° C. In practice, it has been found that a vehicle having a sol-gel transition temperature in the range of from about 25° C. to about 40° C. satisfies this requirement and is useful in the practice of the present invention. Preferably, the sol-gel transition temperature will be in a range of from about 25° C. to about 35° C., and excellent results have been obtained using vehicles having a sol-gel transition temperature in the range of from about 29° to about 31° C.

The capacity of the liquid pharmaceutical vehicle to gel at human body temperatures is the critical feature of the invention for it is in this property that many of the disadvantages of previous approaches are overcome. Thus, the dissipative quality of aqueous solutions is avoided since the vehicles herein gel at the site of treatment. Moreover, the problems of formulation, handling and application of viscous aqueous vehicles or gels are overcome since at the time of application the present pharmaceutical vehicle and composition are free-flowing liquids.

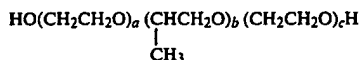
The pharmaceutical vehicle of this invention is clear and water-miscible. These are especially important requirements for usefulness in therapeutic and protective ocular applications. Water-miscibility of the vehicle overcomes major problems faced in attempts to use oily vehicles.

The vehicle of this invention must be physiologically acceptable so that no adverse reaction occurs when the pharmaceutical composition comes in contact with human tissue or fluids. Thus, the vehicles must be inert when tested for ocular tolerance in human and rabbit eyes.

A suitable pharmaceutical vehicle in accordance with this invention comprises an aqueous solution of a selected polyoxyethylene-polyoxypropylene block copolymer. It has been found that polyoxyethylene-polyoxypropylene block copolymers in which the number of polyoxyethylene units is at least about 50% of the number of units in the total molecule, the block copolymer having an average molecular weight of from about 7500 to about 15,500, a room temperature solubility in water greater than about 10 grams per 100 ml. of water, and a cloud point in 1% aqueous solution of at least about 100° C., can be used to form a vehicle composition having a sol-gel transition temperature in the range of from about 25° C. to about 40° C.

Such block copolymers are included in a series of nonionic surface-active agents sold under the trademark "Pluronic" by Wyandotte Chemical Corp. The "Pluronics" are closely related block copolymers that may be generically classified as polyoxypropylene-polyoxyethylene condensates terminating in primary hydroxyl groups. They are formed by the condensation of propylene oxide into a propylene glycol nucleus followed by the condensation of ethylene oxide onto both ends of the polyoxypropylene base. The polyoxyethylene hydrophilic groups on the ends of the molecule are controlled in length to constitute anywhere from 10% to 80% by weight of the final molecule.

The "Pluronic" series of products may be represented empirically by the formula:



where a and c are statistically equal. They have been available in average molecular weights of from about 1100 to about 15,500.

A preferred polyoxyethylene-polyoxypropylene block copolymer for use in the pharmaceutical vehicle of this invention is one in which the number of polyoxyethylene units is about 70% of the total number of monomeric units in the molecule and where the copolymer has an average molecular weight of about 11,500. "Pluronic F-127" is such a material, and it has a solubility greater than 10 gms./100 ml. water as well as a cloud point in 1% aqueous solution higher than 100° C.

The concentration of the polyoxyethylene-polyoxypropylene condensate is an important parameter. Significantly, by ready adjustment of the concentration of the copolymer to accommodate other solutes present in the vehicle, any desired gel transition temperature in the critical range of above ambient temperature and below body temperature can be achieved. Thus, the principal consideration is the selection of a concentration which, in conjunction with all of the constituents of the vehicle composition, will provide a sol-gel transition temperature in the required range.

It has been found that a useful block copolymer concentration is from about 10% to about 26% by weight, particularly from about 17% to about 26%. Excellent results have been obtained using aqueous solutions of from about 17% to about 26% by weight of "Pluronic F-127". The water content is generally from about 74% to about 90% by weight of the vehicle composition, and is typically from about 74 to about 85% by weight. The water used in forming the aqueous solution is preferably purified, as by distillation, filtration, ion-exchange or the like.

The polyoxyethylene-polyoxypropylene pharmaceutical vehicles of this invention have been unexpectedly found to increase drug absorption by the mucous membrane. Moreover, it has also been found that the pharmacologic response is unexpectedly prolonged. Drug action is typically both increased and prolonged by a factor of 2 or more. At the same time, protection is afforded to the involved tissues.

Another advantage is that they are compatible with the therapeutic bandage semi-hard (silicone) and soft or flexible contact lenses. In contrast to drug suspensions in which suspended particles could be lodged in the surfaces of the lenses and cause focal points of irritation or blurred vision, and in contrast to oily vehicles or bases which could adversely affect lens clarity, degree

of hydration, and the physical parameters of therapeutic lenses, the present vehicles, when used in conjunction with therapeutic contact lenses, markedly increased wearing comfort, provided cleaner lenses, and gave more rapid healing responses than without the instillation of the vehicle.

The liquid pharmaceutical vehicles of this invention preferably include at least one water-soluble compatible salt to adjust osmotic pressure. Frequently, the vehicle would be formulated to be isotonic with human serum and tear fluid, the normal tonicity of which is 0.9% (9.0 grams of sodium chloride per liter of vehicle). Isotonic solutions contain about 0.9% sodium chloride, or other salt or mixture of salts having a salt content equivalent to about 0.9% sodium chloride in their osmotic effect.

In general, the vehicles may contain a sufficient amount of at least one salt to provide up to about 10%, especially from about 0.5% to about 6.0%, sodium chloride equivalent salt content. Polyoxyethylene-polyoxypropylene vehicles with as high as 10% sodium chloride equivalent salt content can be made in accordance with this invention having the requisite gel transition temperature. Such compositions are markedly hypertonic, and can be advantageously used where commercially available hypertonic solutions are presently employed.

Generally, it was found that each additional increment of salt proportionately lowered the gel transition temperature.

Any soluble salt or mixture of salts compatible with mucous membrane tissue can be used to provide the desired tonicity. Sodium chloride, potassium chloride, or mixtures thereof, are presently preferred. However, one or more essentially neutral, water soluble alkali metal salts can be substituted in whole or in part for the sodium or potassium chloride in the vehicles of this invention. Thus, other alkali metal halides, such as sodium bromide, potassium fluoride or potassium bromide can be used. Other salts, such as sodium sulfate, potassium sulfate, sodium nitrate, sodium phosphate, potassium nitrate or potassium phosphate can be also be used.

Preferably, the pharmaceutical vehicle contains a compatible preservative or germicide in an amount effective to afford protection to the vehicle against bacterial contamination. Any conventional preservative system may be used.

Quaternary germicides, particularly benzalkonium chloride, are presently preferred. Benzalkonium chloride is an alkyl substituted dimethylbenzylammonium chloride in which the alkyl substituents comprise a mixture of C₈ to C₁₈ alkyl radicals. Exemplary of other preservatives which can be desirably used are salts of ethylenediaminetetraacetic acid, known as edetates, such as disodium edetate and trisodium edetate, sorbic acid, salts of sorbic acid, boric acid, and salts of boric acid, such as sodium borate. Still other useful preservatives or germicides are thimerosal sodium, phenylmercuric acetate, methyl, ethyl and propyl para-aminobenzoic acid esters, and the like.

The preservatives can be used individually or in combination. They are used in effective amount to afford protection against contamination. For example, amounts of from about 0.001% to about 0.03% by weight of a quaternary or organic mercurial germicide are known to be effective and can be used in the present invention. Sorbic acid NF XIII is known to be useful in amounts of from about 0.01% to about 0.5% by weight and may be so used in the present vehicles.

The pH of the pharmaceutical vehicles of this invention may be adjusted as desired. In general, the pH can range from about 3.5 to about 9.5. Preferably, the pH is from about 6.0 to about 8.5, and especially from about 6.2 to about 7.8, the range of the human tear. In some instances, the stability of certain preservatives is maximized by pH adjustment. For example, acid to neutral pH is optimal for the alkyl para-aminobenzoic acid esters.

Compatible, conventional buffers, i.e., weak acids, weak bases, and their corresponding salts, may be used to adjust pH as desired. A sodium biphosphate, disodium phosphate system is exemplary of useful buffering systems. An effective amount of buffer is used to achieve the desired pH. For example, a combination of from about 0.2% to about 0.6% sodium biphosphate and from about 0.2% to about 0.7% disodium phosphate may be used to adjust to a pH in the 6.2 to 7.2 range. Certain preservatives also affect pH, such as trisodium edetate. By selection and simple correlation of the desired additives, one having ordinary skill in the art can readily adjust the pH as desired, while retaining the gel transition temperature in the required range.

Compatible and physiologically-acceptable auxiliary nonionic surfactants may optionally be used to improve solvation of the drug or medicament. Exemplary of conventional surfactants which may be used are Polysorbate 80 and polyoxyl 40-stearate employed in conventional amounts.

Any pharmaceutically active material may be admixed in a pharmacologically effective amount with the pharmaceutical vehicle to form the pharmaceutical compositions of this invention. Preferably, the drug is water-soluble. However, drugs which are not ordinarily soluble in water may also be employed, and it has been found that a wide variety of useful drugs which are currently marketed in suspension form can be dissolved in the polyoxyethylene-polyoxypropylene vehicles of the present invention. Where necessary or desirable, auxiliary nonionic surfactants may be included in the pharmaceutical composition.

The drug or medicament is selected on the basis of the treatment indicated for the patient. Exemplary of drugs which have been used in connection with the pharmaceutical vehicles herein are pilocarpine HCl for glaucoma, phenylephrine for red eyes and Dexamethasone U.S.P. for inflammatory ocular conditions. Various anti-microbial pharmaceuticals for treatment of fungal and viral diseases of mucous membranes may be used, such as Clofazimine, pimaricin, amphotericin, neomycin sulfate, chloramphenicol, bacitracin, sulfacetamide, gentamycin, polymyxin B sulfate, and the like.

The pharmaceutical vehicles and compositions of this invention can be readily prepared. Essentially, any solution forming techniques may be used. The vehicle may be prepared separately and the pharmaceutical added thereto, or preferably, the pharmaceutical composition is formulated without separate preparation of the vehicle. For example, in the use of the polyoxyethylene-polyoxypropylene block copolymer vehicles, the pharmaceutical composition is desirably prepared by fusing the block copolymer, adding the pharmaceutically active material to the fused copolymer, and dissolving the pharmaceutical by simple stirring. A water solution of the remaining ingredients is prepared, and the solution of pharmaceutical in the block copolymer is mixed with the aqueous solution to form a solution of all components. The pH may then be adjusted as desired, e.g., by

addition of a basic or acidic solution as desired. It is generally preferred to add copolymer or a solution of a pharmaceutically active material in the copolymer to the water or aqueous solution rather than adding the water or aqueous solution to the copolymer or copolymer-pharmaceutical mixture.

The pharmaceutical composition is a liquid at ambient temperatures and therefore may be employed in any manner conventionally used to apply free-flowing liquid pharmaceuticals to mucous membranes. Preferably, application is in drop form in the manner typically used, for example, to apply eye drops. Thus, the normal squeeze-type liquid drop application devices are perfectly suitable for use in applying the pharmaceutical compositions of this invention to the site intended for treatment. The amount of pharmaceutical composition should be sufficient to deliver a pharmacologically effective amount of the active pharmaceutical to the mucous membrane treatment area.

In addition to overcoming major disadvantages of previous techniques for delivering drugs and medications to mucous membranes, the present invention has been found to increase drug absorption by the affected tissue and prolong pharmacologic response. Many other advantages will be apparent to those skilled in the art. The general and detailed descriptions of the invention presented above are not intended to be restrictive of the scope of the invention. Rather, in conjunction with the illustrative examples which follow, the description is intended to illustrate the principles of the present invention and specific modes encompassed thereby.

EXAMPLES

The following examples illustrate the compositions of the present invention, and their preparation and utility, but are not limitative of the invention. All percentages are standard weight in volume (W/V) % expressions. In each instance, the formulations were made sterile by using standard heat and pressure techniques, as well as aseptic techniques.

EXAMPLE I

The pharmaceutical vehicle of this invention is exemplified by the composition:

Pluronic F-127	18%
sodium chloride	0.75%
potassium chloride	0.25%
disodium edetate 0.025%	
benzalkonium chloride	0.004%
purified water, enough to make 100% (adjust pH to 7.4 with dilute sodium hydroxide solution)	

It is most easily prepared by mixing all the ingredients in 95% of the required water and allowing the polyoxyethylene-polyoxypropylene copolymer (Pluronic F-127) to hydrate and completely dissolve overnight with gentle stirring at temperatures below 20° C. Once a clear solution is obtained, the pH is adjusted to pH 7.4; and the balance of the water is added. The sol-gel transition temperature was found to be at 29°-30° C.

This vehicle formulation was evaluated on rabbit eyes according to the Draize scoring technique. On a scale having a maximum of 110 possible units of irritation or ocular trauma, experimental values were consis-

tently at or near zero indicating that it produces no adverse ocular effects.

The vehicle itself has pharmacologic utility. It was tested for use in alleviating ocular symptoms of Sjogren's syndrome. Two ophthalmologists treated 11 patients and reported that almost instant relief was obtained.

EXAMPLE II

A variation of the Example I composition was prepared for testing in bullous keratopathy as follows:

Pluronic F-127	17%
benzalkonium chloride	0.0075%
disodium edetate	0.0125%
trisodium edetate	0.025%
sodium chloride	3.75%
potassium chloride	1.0%
purified water, enough to make 100%	

The desired pH is achieved and maintained by the use of the acidic and basic salts of ethylenediaminetetraacetic acid. This formulation contains approximately five times the amount of salt present in isotonic sodium chloride solution. The solgel transition temperature was about 30° C.

When the formulation was tried in 6 patients, with and without soft contact lenses, and all with corneal edema associated with bullous keratopathy, very significant improvement was noted. In several other instances where corneal swelling was associated with prolonged hard contact lens wear, as well as other edematous conditions of unrelated problems, the product was found efficacious. When compared to Adsorbonac 5 (Burton Parsons, Inc., Washington, D.C.), a commercially available hypertonic solution, the new invention was preferred in all instances. The test preparation caused significantly less discomfort upon eye instillation.

EXAMPLE III

The following vehicle was prepared:

Pluronic F-127	16%
sorbic acid	0.1%
disodium edetate	0.1%
sodium borate	0.23%
sodium chloride	0.5%
potassium chloride	0.2%
purified water, enough to make 100%	

The pH was 7.5, and the sol-gel transition temperature was 34° C. With the advent of continuous wear therapeutic soft contact lenses, and more recently continuous wear cosmetic lenses, there is a frequent need for innocuous eye drops that loosen the accumulated mucoid deposits on the lenses, reequilibrate the lenses and add to the overall comfort of wear. The composition of this Example was evaluated by an ophthalmologist for this purpose by eye drop application on 14 patients. Without exception, all of the patients found that this eye drop was the best product which they had used. The ophthalmologist was also impressed with the clinical response.

Examples I, II and III illustrate compositions which may be used as pharmaceutical vehicles in accordance with the invention, and significantly, have protective

and therapeutic usefulness in themselves without further addition of drugs or medicaments. The following Examples demonstrate preparation and utility of pharmaceutical compositions in accordance with the invention.

EXAMPLE IV

The following pharmaceutical composition containing the drug Dexamethasone as the added active pharmaceutical material was prepared to test corticosteroid anti-inflammatory solubilization and stability:

Dexamethasone U.S.P.	0.05%
Pluronic F-127	19%
thimerosal sodium U.S.P.	0.005%
disodium edetate U.S.P.	0.1%
sodium chloride U.S.P.	0.9%
purified water U.S.P., enough to make 100%	

To prepare this formulation, the Pluronic F-127 was first fused at about 50°-60° C., at which point the Dexamethasone was added and dissolved by simple stirring. The remainder of the ingredients were dissolved in water and added. Then the pH was adjusted to 7.0 with the dilute solution of sodium hydroxide. The solution, observed over a period of 5 months, remained crystal clear. The sol-gel transition temperature was about 26° C. On warm days, refrigeration was required to maintain the product in the liquid state. However, this turned out to be advantageous for when the cooled product was tried on 2 patients with a severe inflammatory ocular condition resulting from chemical burns, the cooling sensation upon instillation provided added relief. Other clinical tests of this formulation verified its utility and demonstrated that the concentration herein employed, which is half of the amount normally used in the commercially available product Decadron (Merck, Sharpe & Dohme), was at least as effective. Using half as much of an expensive raw material could mean a significant saving to the patient.

EXAMPLE V

The following pharmaceutical composition containing pilocarpine HCl as the added active pharmaceutical was prepared for treatment of glaucoma:

pilocarpine HCl	0.5%
Pluronic F-127	18%
sodium chloride	0.3%
potassium chloride	0.1%
disodium phosphate	0.5%
sodium biphosphate	0.08%
benzalkonium chloride	0.01%
purified water, enough to make 100%	
pH - 6.8	

This formulation was compared to 2% pilocarpine (commercially available in an aqueous solution) normally prescribed for glaucoma in 4 patients. In all instances, the reduction in intra-ocular pressure by treatment with the present formulation was found to be as good as or better than the product having four times the concentration.

EXAMPLE VI

The following composition containing phenylephrine HCl as the added pharmaceutically active material was prepared:

phenylephrine HCl	0.1%
Pluronic F-127	18%
sodium chloride	0.9%
benzalkonium chloride	0.008%
purified water, enough to make 100%	

This formulation was compared to an aqueous 0.5% solution in a small series of patients with red eyes. The rate of vasoconstriction (scleral blanching) in both instances was about the same. Two of the 3 volunteer patients reported better comfort in the eye treated with the present formulation. In all 3 patients, the paired eyes treated with this product looked much better than the 0.5% phenylephrine solution when examined with a slit lamp 20 minutes after treatment. Residual amounts of the pharmaceutical vehicle were still apparent in the treated eyes, whereas all of the more concentrated 0.5% aqueous solution had dissipated in the opposite eyes. This observation demonstrates the added ocular protection and duration of the new drug form of this invention.

EXAMPLE VII

The following pharmaceutical solution containing the antimicrobial agent Clofazimine was prepared:

Clofazimine	0.1%
Pluronic F-127	12%
Polysorbate 80	20%
sodium chloride	0.6%
benzalkonium chloride	0.1%
purified water, enough to make 100%	
pH - 6.8, sol-gel transition at 35° C.	

This pharmaceutical composition was tested in vitro and found to exhibit good activity.

EXAMPLE VIII

The following pharmaceutical solution containing the antimicrobial agent pimaricin was prepared:

pimaricin	0.3%
Pluronic F-125 (average molecular weight of about 8000, polyoxyethylene units about 50% of total units in molecule)	10%
polyoxyl 40-stearate	20%
sodium chloride	0.6%
benzalkonium chloride	0.1%
purified water enough to make 100%	
pH - 6.5, sol-gel transition at 31° C.	

This formulation was also tested in vitro and was likewise found to exhibit good activity.

Pharmaceutical compositions containing antimicrobial agents other than those of Examples VII and VIII have similarly been prepared and tested with success.

Suitable vehicles for antimicrobial agents have been a recognized problem, and the usefulness of the vehicles of this invention in connection with antimicrobial agents represents a particularly significant and advantageous aspect of this invention.

It will be readily apparent to those skilled in the art that the features, advantages and uses of this invention are many. Those skilled in the art will recognize that many modifications and adaptations of the invention can be made without departing from the scope or spirit of the invention.

What is claimed is:

1. A pharmaceutical composition for medicinally treating a mucous membrane or eye condition requiring pharmacologic treatment, comprising:

(a) a pharmacologically effective amount of a chemical material which is pharmacologically active against said condition; said material being selected from the group consisting of dexamethasone, pilocarpine HCl, phenylephrine HCl, clofazimine, pimaricin, amphotericin, neomycin sulfate, chloramphenicol, bacitracin, sulfacetamide, gentamycin, and polymixin B sulfate;

(b) from about 10% to about 26% by weight of a polyoxyethylene-polyoxypropylene block copolymer in which the number of polyoxyethylene units is at least about 50% of the total number of monomeric units in the total molecule, the block copolymer having an average molecular weight of from about 7,500 to about 15,500, a room temperature solubility in water of greater than about 10 grams per 100 ml. of water, and a cloud point in 1% aqueous solution of at least about 100° C.;

(c) up to about 10% sodium chloride equivalent of at least one water-soluble compatible salt selected from the group consisting of sodium halide, sodium sulfate, sodium nitrate, sodium phosphate, potassium halide, potassium sulfate, potassium nitrate, potassium phosphate, and mixtures thereof;

(d) an effective amount of a preservative to afford protection to the composition against bacterial contamination selected from the group consisting of benzalkonium chloride, a sodium salt of ethylenediaminetetraacetic acid, sorbic acid, and alkali metal salt of sorbic acid, boric acid, an alkali metal salt of boric acid, thimerosal sodium, phenylmercuric acetate, a methyl, ethyl or propyl ester of para-aminobenzoic acid, and mixtures thereof; and

(e) from about 74% to about 90% by weight water; the composition having a pH of from about 6.0 to about 8.5 and a gel transition temperature in the range of from about 25° C. to about 40° C.

2. A pharmaceutical composition according to claim 1 in which the copolymer constitutes from about 12% to about 26% by weight, has an average molecular weight of about 11,500, and the number of polyoxyethylene units is about 70% of the total molecule, and in which the gel transition temperature is in the range of from about 25° C. to about 35° C.

3. A pharmaceutical composition according to claim 1 in which the pH is from about 6.2 to about 7.8.

4. A pharmaceutical composition according to claim 1 in which the liquid composition has a gel transition temperature in the range of from about 29° C. to about 31° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,188,373
DATED : February 12, 1980
INVENTOR(S) : JOSEPH Z. KREZANOSKI

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 2, line 65, "thylenepolyoxypropylene" should read
-- thylenepolyoxypropylene --.

Column 8, line 51, "0.025%" should be in the percent column.

Column 9, line 25, "solgel" should read -- sol-gel --.

Column 11, line 35, "12%" should be in the percent column.

Column 11, line 36, "20%" should be in the percent column.

Column 11, line 51, "10%" should be in the percent column.

Column 11, line 56, "20%" should be in the percent column.

Signed and Sealed this

Twenty-second **Day of** *July 1980*

[SEAL]

Attest:

SIDNEY A. DIAMOND

Attesting Officer

Commissioner of Patents and Trademarks



US005256396A

United States Patent [19]**Piechota, Jr.**[11] **Patent Number:** **5,256,396**[45] **Date of Patent:** **Oct. 26, 1993**[54] **TOPICAL COMPOSITION**[75] **Inventor:** **Stanley E. Piechota, Jr., Somerset, N.J.**[73] **Assignee:** **Colgate-Palmolive Company, Piscataway, N.J.**[21] **Appl. No.:** **469,198**[22] **Filed:** **Jan. 24, 1990**[51] **Int. Cl.⁵** **A61K 7/16; A61K 7/18; A61K 7/22**[52] **U.S. Cl.** **424/49; 424/52; 424/54**[58] **Field of Search** **424/49-58; 514/944**[56] **References Cited****U.S. PATENT DOCUMENTS**

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4,843,099 6/1989 Gaffar 514/576**OTHER PUBLICATIONS**Schmolka, *Cosmetics & Perfumery*, Apr. (1974), 63.
Pader, *Surfactants in Cosmetics*, Surfactant Science series, (1985), pp. 306-307.
BASF Brochure *Pluronic & Tetronic Surfactants*, (1987), p. 17.*Primary Examiner*—Shep H. Rose
Attorney, Agent, or Firm—Paul Shapiro; Robert C. Sullivan[57] **ABSTRACT**

In accordance with the teachings of this invention, a composition and method for the topical application of a water dispersible active ingredient to a surface of a warm blooded animal is provided. Specifically, such composition is provided to have the properties of being readily flowable upon filling a container therewith, maintaining such flowable condition after storage for a substantial length of time and being readily flowable upon application to the desired animal situs. Uniquely, upon contact with the warm surface of the animal then, and only then, does the composition quickly forms into a non-flowable relatively substantive gel. Specifically such composition comprises:

- (a) a water soluble non-ionic block copolymer of ethylene oxide and propylene oxide of the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_c\text{H}$;
(b) the active ingredient to be topically delivered; and
(c) water.

7 Claims, No Drawings

TOPICAL COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates generally to the provision of compositions for the topical application of a water soluble active ingredient to a surface of a warm blooded animal including humans. In particular, this invention relates to such a composition which can be applied as a relatively low viscosity flowable liquid and which will quickly, upon contact with the warm surface of such animal, turn into a relatively high viscosity, essentially non-flowable, gel.

The field of applying active ingredients topically to humans and animals is, of course, wide ranging and comprises for example, the application of active ingredient for therapeutic, prophylactic and cosmetic purposes. Notwithstanding this wide and varying range of purposes, a great many of such applications suffer from a common problem. Specifically, it is desirable to provide such compositions in a pourable, flowable liquid form so that containers for the composition can easily be filled, the composition can easily be dispensed from such containers and the composition can easily be applied to the desired situs; either by mechanical means e.g., a syringe and needle, a spray or pump, or by hand. On the other hand, once the composition has been packaged, dispensed and applied to the situs, it is desirable that the composition no longer flow but instead remain in place and release the active ingredient.

As an example, it is desirable to topically apply certain therapeutic liquids into subgingival pockets in the treatment of periodontal disease. Injection devices employed for the purpose utilize fitments with small orifices to enable the injection tip to fit into the subgingival pocket easily without inflicting excessive pain to a patient. An example of such a device is described in U.S. Pat. No. 4,617,918. Clearly, to flow through the small orifices of such devices, the composition must be of relatively low viscosity and easily flowable. Once delivered to the subgingival pockets, however, it is desirable that the composition remain in place and deliver the medicament to the affected tissue. A low viscosity fluid will obviously not suffice for this purpose.

The problem of providing a composition having these apparently contradictory properties (i.e., flowable during filling, dispensing and applying while non-flowable after being applied to the desired situs) has been addressed in U.S. Pat. No. 4,411,889 to Caslavsky, et al. This specification teaches the provision of a composition for topical delivery of fluoride or antibacterial agents to the oral cavity and employs a composition said to be a low-viscosity, aqueous solution adapted to be converted, after mixing and topical application, from a liquid solution to a gel state. The operative ingredients in this invention comprise a silica acid ester monomer or prepolymer which on hydrolysis forms silica polymer when in the presence of one or more gelling agents such as gel catalysts or silicate esters. The gelling is initiated and it is taught that from anywhere from 24 hours to less than one minute after combining the gelling agent with the remainder of the composition, gelling is effected. Thus while the composition accomplishes the result of in situ gelling after application, in practice, several drawbacks are manifested. In use, it is incumbent upon the applicator to first mix the composition with the gelling agent and hence requires weighing and/or measuring and mixing; operations which are clearly

inconvenient to a professional and totally impractical to a lay consumer. Moreover, there is an exquisite timing requirement in using such compositions: the mixing must occur closely enough to application so as to provide sufficient working time prior to gelling and yet upon application the composition must gel quickly enough to realize the benefits of an applied gel. Such precise timing once again represent great inconvenience for the professional and essentially precludes use by the lay user.

Accordingly, there is a need for a composition which can be filled and stored, as a flowable liquid, dispensed as a liquid and, without the need for any further mixing or measuring, applied to a desired situs where it will quickly form, in situ, into a gel.

SUMMARY OF THE INVENTION

In accordance with the teachings of this invention, an oral composition and method for the topical application of a water dispersible active ingredient to a surface of a warm blooded animal is provided. Specifically, such composition is provided to have the properties of being readily flowable upon filling a container therewith, maintaining such flowable condition after storage for a substantial length of time and being readily flowable upon application to the desired animal situs. Uniquely, upon contact with the warm surface of the animal then, and only then, does the composition quickly forms into a non-flowable relatively substantive gel. Specifically such composition comprises:

- (a) a water soluble non-ionic block copolymer of ethylene oxide and propylene oxide of the formula



- (b) the active ingredient to be topically delivered; and
- (c) water.

The block copolymer is preferably chosen (with respect to a, b, and c) such that the ethylene oxide constituent comprise from about 65 to about 75%, by weight, of said copolymer molecule and the copolymer has an average molecular weight of from about 11,000 to about 13,000 and with said copolymer being provided in such quantity that the composition is flowable at temperatures below 80° F. (26.7° C.) and forms a gel upon contact with the surface of such warm blooded animal. Preferably, the weight percent of the copolymer in the composition should be greater than ten percent and not less than twenty percent and still more preferably from about twelve to about seventeen percent.

The above described composition will maintain a low viscosity and be relatively flowable at temperatures below about 80° F. (26.7° C.). Upon contact with the surface of a warm animal having a body temperature above 80° F. (26.7° C.) e.g., 98° to 99° F. (36.7°-37.2° C.), as in a human, the composition will gel within seconds and cease to flow without the application of substantial force.

The invention finds particular use as a liquid dispersion for the topical application of active ingredients to the oral cavity. Further, in another aspect of the invention the composition may be employed to facilitate the application of an active ingredient to a warm surface, e.g. when the active ingredient to be applied by first dispensing the composition onto the applicator's hand. In accordance with the teachings herein, such composition will be dispensable onto the warm surface as a flowable

liquid and then gel so as to preclude undesirable dripping from such surface. Thus for example the composition may be dispensed onto an applicator's hand where it will gel and facilitate further application.

The ethylene oxide/propylene oxide block copolymer of the composition of the invention is selected from a group of water soluble polyalkylene glycol block copolymers known generically as poloxamers.

In accordance with the teachings of this invention the poloxamer chosen is one in which the ethylene oxide units constitute from about 65 to about 75%, by weight of said copolymer molecule. The copolymer has an average molecular weight of from about 11,000 to 13,000 and preferably from about 12,000 to about 13,000. The poloxamer of choice is designated poloxamer 407 and has an average molecular weight of about 12,500. The poly(ethylene oxide) blocks average 67 moles, i.e. about 60%, by weight. Poloxamer 407 as described by the manufacturer is nontoxic, exhibiting in rat studies an LD₅₀ of 15.4 g/kg and in studies with rabbits, an acute dermal toxicity greater than 2 g/kg. An aqueous solution of 20% by weight of Poloxamer 407 was found by the manufacturer to be non-irritating in a Draize Rabbit Eye irritation study. Table 1 set out some of the physical properties of this preferred poloxamer 407 as sold by the BASF Wyandotte Corporation of Parsippany N.J. under the trademark PLURONIC F127.

TABLE 1

Physical Properties of Poloxamer 407	
Average molecular weight	12,600
Melt Point	56° C.
Physical Form at 20° C.	Solid
Brookfield Viscosity at 77° C.	3100 cps.
Surface tension at 25° C., 0.1%	41 dynes/cm.
<u>Draves Wetting at 25° C.</u>	
1.0%	>360
0.1%	>360
Foam Height	40 mm
(Ross Miles 0.1%, aqueous at 50° C.)	
<u>Cloud Point in aqueous Solution</u>	
1.0%	>100° C.
10%	>100° C.
HLB (hydrophilic lipophilic balance)	18-23

Poloxamer 407 is virtually tasteless and odorless and hence has found use in solubilization of aromatics in oral hygiene products such as aqueous alcoholic mouthwashes. As usual in these compositions, the concentration is quite low (less than 10% by weight and generally less than 1% by weight) and hence such compositions do not exhibit the self gelling properties described herein. The poloxamer compounds are indeed known to be useful in forming gels and, in fact are so described in a brochure of the aforementioned BASF Corporation entitled Pluronic & Tetronic Block Copolymers Surfactant pp. 16-17 (1987). In a further publication of BASF entitled Technical Data of Pluronic Polyols, the recommended procedure is described for forming gels from Pluronic F127 solutions. It is said that gels will be formed with concentrations having a minimum of 20% by weight of such compound and may be formed by dissolving the Pluronic F127 at 80° C. into the solution and cooling to room temperatures to form the gel. Alternatively, the Pluronic® F127 may be dissolved into a water solution at 5° to 10° C. and then brought to room temperature whereupon it forms a ringing gel. As is apparent, these teachings would not lead one skilled in the art to employ Pluronic F127 to meet the objects

of this invention in that such teachings are totally inimical to the objects of this invention; it is taught that the result is a gelled solution at room temperature i.e., one that cannot be filled, stored or dispensed as a flowable liquid.

Instead, it has now been discovered that by employing poloxamer 407, in concentrations untaught by the prior art namely, greater than ten percent and less than twenty percent and preferably from twelve to seventeen percent) an aqueous single phase solution is produced which is liquid and flowable at room temperature and will gel in only a few seconds when elevated to about 80° F. Specifically, it has been discovered that such a composition having such properties will result if the poloxamer is poloxamer 407 and is employed in concentrations heretofore untaught by the prior art namely, of greater than ten percent and less than twenty percent. Preferably such concentration should range from about twelve to about seventeen percent. While the mechanism for the phenomenon of gelling at the desired temperature is not completely clear, it is believed that such behavior is totally dependent on the choice of a specific narrow range of defining parameters for the polymer e.g., molecular weight and proportions of ethylene oxide to propylene oxide units together with the choice of a narrow band of concentrations of the polymer in the composition.

The teachings of this invention are broadly applicable to a large number of aqueous compositions intended to deliver active ingredients to the situs of a warm animal. Such compositions may include therapeutic compositions wherein the active ingredient is a medicament as, for example, the topical delivery of resorcinol for treating various dermatological conditions, the delivery of adrenocorticoids as an antiinflammatory or the use of retinoids in acne treatment. A specific example of this is described in U.S. Pat. No. 4,843,009 wherein Ibuprofen is delivered to the oral cavity. The composition may be employed to deliver active ingredients for prophylactic purposes e.g. an antiseptic or antimicrobial agent. The invention is equally applicable for delivery active ingredients for cosmetic purposes e.g. as a cooling lotion or astringent or for delivery of perfumes or deodorants.

A particularly useful employment of the teachings of this invention is a liquid dispersion e.g., a mouthwash, for delivering prophylactic or therapeutic active ingredients to the oral cavity. Such active ingredients may include antimicrobial and antibiotic agents e.g. triclosan, chlorhexidine, alexidine, cetylpyridinium chloride or sanguinarine as well as essential oils, fluorides providing anticaries properties, astringents such as zinc compounds. Some typical anti-microbial agents are set out with greater particularity in commonly assigned copending British patent application 8801773, published as GB 2200551A on Aug. 10, 1988. Such active ingredients may also include astringent salts which form a thin protective film on the surface of body cells and hence lessen the cells sensitivity to external stimuli such as might be caused by mechanical, thermal or chemical action. Examples of astringent compounds utilized in orally applied compositions include zinc salts such as zinc chloride and zinc citrate which are soluble in water. Such active ingredient may also include certain compounds for the purpose of topical deodorization such as, for example, chlorophyllins. Additionally, such active ingredient may include fluorides as anticaries agents such as sodium fluoride, stannous fluoride, sodium monofluorophosphate, and the like. It will be

understood that the above recitation of active ingredients is merely exemplary and that many others will occur to one skilled in the art as usable within the teachings of this invention.

In addition to such active ingredients, additional components are typically employed in oral aqueous compositions including such additional components as alcohol, flavor, humectants and surfactants.

Alcohols are employed, in denatured form, in concentrations of about 5 to about 30% for the various purposes of enhancing the impact of a flavor ingredient, enhancing antimicrobial efficacy or for facilitating the solubility of other ingredients. Suitable alcohols are for example ethanol or isopropanol.

Flavors utilized in mouth washes for example, include such ingredients as eucalyptol, menthol, thymol, methyl salicylate together with flavor modifiers. Additionally, certain mint-type flavors and cinnamon type flavors have been employed including for example peppermint, spearmint or clove. Frequently, sweeteners such as saccharin compounds are also included.

Humectants are employed primarily to prevent crystallization around closures. Glycerin sorbitol, polyethylene glycol, and polypropylene glycol being generally the humectants of choice.

Additionally, as has been described above, surfactants have been employed, primarily to aid in the solubilization of some of the other ingredients and to provide a foaming action if desired. In addition to the poloxamer compounds described above, such surfactants may include other non-ionics such as polyethylene fatty acid esters, and sorbitan monostearate as well as cationics such as cetylpyridinium chloride or anionics such as sodium lauryl sulfate.

The invention may also be employed in a cosmetic preparation such as an after shave lotion where the active ingredient is essentially a denatured alcohol. Other ingredients in such a composition may include perfumes and coloring agents.

DESCRIPTION OF CERTAIN EMBODIMENTS

The following examples are further illustrative of the nature of the present invention. All amounts and properties referred to herein are by weight.

EXAMPLE 1

An antimicrobial mouthrinse is prepared comprising chlorhexidine digluconate as the active antimicrobial agent.

Ingredient	Weight Percent
Deionized Water	78.98
Ethanol (190°)	5.00
Sodium Saccharin	0.20
Hibitane (20% Chlorhexidine digluconate)	0.12
Pluronic F-127	15.00
Flavor 89-180	0.10
FD&C Blue #1 (0.1% Sol.)	0.30
FD&C Yellow #5 (0.1% Sol.)	0.30
	100.00

This composition is a flowable liquid at temperatures below 82° F. (27.8° C.), and when heated to 82° F. the composition gels in less than one minute. The sample gels upon contact with the oral surface.

EXAMPLE 2

An antimicrobial mouthrinse is prepared comprising cetylpyridinium chloride as the active antimicrobial agent.

Ingredient	Weight Percent
Deionized Water	79.00
Sodium Saccharin	0.20
Ethanol (190°)	5.00
Cetylpyridinium Chloride	0.10
Pluronic F-127	15.00
Flavor 89-180	0.10
FD&C Blue #1 (0.1% Sol.)	0.30
FD&C Yellow #5 (0.1% Sol.)	0.30
	100.00

Again, this composition is a flowable liquid below 82° F. and when heated to 82° F. (27.6° C.), gels in less than one minute. The sample gels upon contact with the oral surface. Accordingly, the use of alternative antimicrobial agents does not effect the desired gelling phenomenon.

What is claimed is:

1. An oral composition for the topical application of a water dispersible active ingredient to a surface of a warm blooded animal comprising:

(a) a water soluble, nonionic block copolymer of ethyleneoxide and propylene oxide of the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_c\text{H}$, wherein the ethylene oxide units comprise from about 65 to about 75% by weight of said copolymer and said copolymer has an average molecular weight of from about 11,000 to about 13,000; the copolymer comprising more than 10 to about 17% by weight of said composition;

(b) said active ingredient; and

(c) water; said composition being flowable at temperatures below 80° F. and forms a gel upon contact with said oral surface of said warm blooded animal.

2. The composition of claim 1 wherein said copolymer has an average molecular weight of from about 12,000 to about 13,000.

3. A liquid dispersion for the topical application of active ingredients to the oral cavity comprising:

(a) a water soluble, nonionic block copolymer of ethylene oxide and propylene oxide of the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_c\text{H}$, wherein the ethylene oxide units comprise from about 65 to about 75% by weight of said copolymer and said copolymer has an average molecular weight of from about 11,000 to about 13,000; the copolymer comprising from more than 10 to less than 17% by weight of the composition.

(b) said active ingredient, selected from one or more of the group consisting of antimicrobial agents, anticaries fluorides, astringents, and topical deodorizers; and

(c) water; said composition being flowable at temperatures below 80° F. and forms a gel upon contact with warm surfaces of the oral cavity.

4. The composition of claim 3 wherein said copolymer has an average molecular weight of from about 12,000 to about 13,000.

5. A method for the facile application of an active ingredient to the oral cavity comprising:

(a) maintaining an aqueous dispersion of said active ingredient at a temperature below 80°F., said aque-

ous dispersion comprising a water soluble, non-ionic, block copolymer of ethylene oxide and propylene oxide of the formula $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_c\text{H}$ wherein the ethylene oxide units comprise from about 65 to about 75% by weight of said copolymer and said copolymer has an average molecular weight of from about 11,000 to about 13,000; the copolymer comprising from more than 10 to about 17% by weight of the composition, the composition being flowable at temperatures below

80° F. and forms a gel at temperatures above 80°F.; and

(b) applying said aqueous dispersion to the oral cavity to form such gel.

5 6. The method of claim 5 wherein said copolymer has an average molecular weight of from about 12,000 to about 13,000.

10 7. The method of claim 5 wherein the active ingredients are selected from one or more of the group consisting of antimicrobial agents, anticaries fluorides, astringents and topical deodorizers.

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Dobrozsi et al.

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(54) **POURABLE LIQUID VEHICLES**

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(52) **U.S. Cl.** **514/772.4; 424/485; 424/486**

(58) **Field of Search** **424/426, 78, 177, 424/485, 486; 514/772.4**

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(57) **ABSTRACT**

The present invention covers pourable liquid vehicles that can be combined with compositions, materials and substances. Among the benefits of such pourable liquid vehicles is the compositions are retained on the moistened surface for a period of time sufficient to allow compositions, materials and substances to act on said surface, resisting erosion or run-off from additional moisture being applied. Such pourable liquid vehicles have a number of utilities including but not limited to cleaning and treating surfaces of objects as well as biological or living organisms, including living creatures.

27 Claims, No Drawings

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POURABLE LIQUID VEHICLES

CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(c) from Provisional Application Serial No. 60/153,260, filed Sep. 11, 1999.

TECHNICAL FIELD

Concentrated levels of polyoxyalkylene block copolymers are useful in vehicles incorporated into products that are designed to deliver compositions, materials and substances to moistened surfaces and aqueous environment. Acquiring moisture during use, the vehicle becomes sufficiently transformed from a liquid to a gel-like form that provides a benefit to the user. For example, mucosal surfaces of the body contain sufficient water to allow the pourable liquid vehicle comprising concentrated polyoxyalkylene block copolymers to be effectively delivered to the desired site wherein the accompanying compositions, materials and substances tenaciously adhere to the moistened surfaces and resist dissolution or erosion by water or biological fluid. Such uses include, but are not limited to the delivery of personal health care compositions, formulations and compounds including, but not limited to, pharmaceuticals (OTC and prescription), nutrients and the like.

In the discipline of pharmaceutical compositions there are a wide variety of dosage forms. Examples include tablets, capsules, clixirs, syrups, liquid-filled capsules, suspensions, coated tablets or capsules for administration by mouth; gels, rinses, dentifrices, lozenges, sprays, medicated lollipops, liquid filled capsules for intra-oral administration; gels, suspensions or solutions for intra-ocular or intra-aural administration; suppositories and douches or enemas for intra-rectal or vaginal administration; and creams, ointments, gels, lotions and patches for topical application on the skin and scalp; and liquid suspension or solutions for injection by syringe, nasal gels, solutions, or suspensions for application into the nose with special applications or sprays.

The majority of these compositions are in the physical form of a fluid having a viscosity ranging from pourable liquids to stiff gels. Pourable liquids are often preferred since they are in the best form to be administered. For example, only liquids, or perhaps low viscosity gels, can be injected through a syringe, or poured from a bottle into a medicine cup, or drawn up into a syringe or medicine dropper, or squeezed from a dropper bottle into the eye or ear, or atomized into the nasal cavities. In addition to the compatibility with pharmaceutical administration devices and with the mode of introduction into the body, it is often desirable for the composition to easily spread after application without the aid of manual action or devices. The eye drop compositions, for example, need to spread over the surface of the eye, as do swallowed liquids intended to coat the throat, esophagus, or stomach. This is similarly true of rectal enemas or vaginal douche compositions.

In many cases, however, pharmaceutical dosage forms in form of pourable liquids are not necessarily desirable since once administered, such pourable liquids are easily removed from the intended treatment site. In such circumstances the therapeutic advantage of the composition may be significantly diminished or even lost completely. It is appropriate, therefore, to surmise that for the purpose of being retained at the targeted site, it may be desirable for a particular pharmaceutical composition to be more viscous, even in the form of a gel that is not readily flowable. It is, however,

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difficult or even impossible to administer such a viscous composition to its intended site to do the most good. For example, serious injury could occur when attempting to spread a gel on the surface of one's eye using a finger or more elaborate applicators. More problematic is coating the stomach lining, as this site is simply not accessible using simple self-administer applicators.

There is, therefore, a need for pharmaceutical compositions that are "smart"; that is, capable of being administered in a pourable liquid that are converted or transformed after administration into a vehicle having sufficient viscosity to essentially remain at the targeted site. Such compositions require a built-in chemical or physical triggering mechanism(s) that respond to conditions after application in or on a surface including the body.

BACKGROUND OF THE INVENTION

Attempts to develop such compositions have been ongoing for a significant period of time. Examples of such compositions include intra-ocular dosage forms as disclosed in Edsman, K., Carlfors, J., Petersson, R., *Rheological Evaluation of Poloxamer as an In Situ Gel for Ophthalmic Use*, European Journal of Pharmaceutics Vol. 6 pp.105-112 (1998) herein incorporated by reference. Compositions such as these are broadly described as primarily aqueous solutions of block co-polymer surfactants, other wise referred to as "poloxamers", that are commonly known in the art. When formulated in water as somewhat concentrated solutions, or with water and co-solvents, the poloxamer solution remains as a pourable liquid. The most commonly reported example of this type of system consists of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water. These compositions are administered at room temperature as liquids. They form a gel upon reaching body temperature. The trigger for converting these compositions to a gel, therefore, is body heat.

In situ gelation of pharmaceutical compositions based on poloxamer that are biologically triggered are known in the art. For example Kim, C. K., Lee, S. W., Choi, H. G., Lee, M. K., Gao, Z. G., Kim, I. S., and Park, K. M.: *Trials of In Situ Gelling and Mucoadhesive Acetaminophen Liquid Suppository in Human Subjects*, International Journal of Pharmaceutics vol. 174, pp. 201-207 (1998) incorporated herein by reference. Kim et al. discloses liquid suppositories for enhancing absorption of the pain and fever relieving drug acetaminophen.

U.S. Pat. No. 5,256,396, issued Oct. 26, 1993, to Colgate Palmolive Company, incorporated herein by reference, describes similar compositions containing poloxamer 407 and water at specified concentrations. Other products utilizing bio-triggers include those comprising poloxamer 407 at ranges preferably 12% to 17%. When combined with pharmaceutically active agents, these compositions are injected into the gingival space between the root of a tooth and the gum.

Poloxamers represent a large family of polymers that vary in molecular weight as well as in the percentage or portion of the block copolymer that is considered hydrophobic. Compositions comprising other poloxamers from this family having similar liquid/gelling characteristics are somewhat predictable, lacking only in the understanding of the required concentration of poloxamer. While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions. Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments.

SUMMARY OF THE INVENTION

The present invention covers pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments. The benefits of compositions formulated with such pourable liquid vehicles include retention of the compositions, materials and substances on the moistened surface. This in turn allow for effective delivery of a desired composition, material and substance in the vehicle that acts on targeted surface, resisting erosion or run-off even in an aqueous environment. Such pourable liquid vehicles have a number of utilities for delivery of all kinds of materials including but not limited to cleaning and treating surfaces of objects as well as biological or living organisms, including living creatures.

Another object of this invention is to utilize such pourable liquid vehicles to deliver health care compositions and materials and substances to living creatures, particularly mammals, and most particularly humans. Even another object of the present invention is to develop a method for effective delivery of health care compositions, materials and substances.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Terms useful herein are defined below. Additionally, terms used in the art, as well as general concepts, are further described in Schramm, *The Language of Colloid and Interface Science*, American Chemical Society, (1993), incorporated herein by reference.

The term "pourable liquid" as used herein means the physical state of the compositions of the present invention prior to formation of a gel.

The term "moistened surface" as used herein means any living or non-living surface having sufficient moisture in or on it to trigger rapid conversion of a pourable liquid to a gel.

The term "in situ gelation" as used herein means the conversion of a pourable liquid to a gel at a designated site or surface.

As used herein, the term "gel" describes the substance resulting from the combination of the pourable liquid and water, or bodily fluid containing mostly water. The gel is sufficiently viscous to remain at the site applied to, or ultimately targeted for, over a period of time sufficient for the compositions, materials and substances in the gel to bring about a desired result at the site they are delivered to.

The term "triggering device" as used herein means a stimulus external to the composition that induces the conversion of a pourable liquid to a gel.

The term "shear" as used herein is the rate of deformation of a fluid when subjected to a mechanical shearing stress. In simple fluid shear, successive layers of fluid move relative to each other such that the displacement of any one layer is proportional to its distance from a reference layer. The relative displacement of any two layers divided by their distance of separation from each other is termed the "shear" or the "shear strain". The rate of change with time of the shear is termed the "shear rate".

A certain applied force is needed to produce deformation in a fluid. For a plane area around some point in the fluid and in the limit of decreasing area the component of deforming forces per unit area that acts parallel to the plane is the "shear stress".

The "viscosity" of a viscous material, also called viscosity index, is defined as the ratio of the shear stress applied into

the material, divided by the rate of shear which results. Materials of a higher viscosity have a higher resistance to flow, or to forces which can induce flow, than a lower viscosity material. All viscosities listed herein are at a shear rate of about 50 per second unless otherwise indicated. All of the rheologic characteristics given herein can be measured in a controlled rate or a controlled stress rotational viscometer capable of some operation in a controlled rate mode, for Example Haake RS 150 by Haake GmbH, Karlsruhe, Germany; Carrimed CSL 500 Controlled Stress Rheometer by TA Instruments, New Castle, Delaware; and Rheometric SR5, by Rheometric Scientific, Piscataway, N.J.

Specifically, when subject to constant shearing rate of about 50 per second at normal ambient temperature (approx. 25° C.), the present liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds.

The value of a composition's triggered viscosity ratio ("T") is useful in determining the degree to which a composition exhibits the above described gelling characteristic. The formula and procedure for determining the triggered viscosity ratio is set forth below.

It is desirable for the compositions of the present invention to exhibit a triggered viscosity ratio of at least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10 wherein the triggered viscosity is defined by the following formula or ratio:

$$T = \eta_g / \eta_l$$

where η_g = viscosity of the gel and

where η_l = viscosity of the pourable liquid

The pourable liquid vehicle of the present invention must be selected and formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture. Examples of these fluids are saliva, gastric fluid, intestinal fluid, extracellular fluid present under the skin at the site of a subcutaneous injection, or in muscle tissue at the site of an intramuscular injection, cerebrospinal fluid, vaginal fluid, fluid exudate from an open wound or ulcer, tear fluid, rectal fluid, or any other bodily fluid of an animal which contains in large measure water. In other words, after the pourable liquid vehicle contacts with the bodily fluid, the viscosity of the pourable liquid vehicle becomes greater than the viscosity of either the pourable liquid vehicle itself prior to mixing, or the bodily fluid alone.

The triggered viscosity ratio of a pourable liquid vehicle can be determined by one skilled in the art using appropriate viscosity measuring instruments, and is exemplified by the following method. First, the viscosity of the pourable liquid vehicle (η_l) is determined in a rheometer using a shear rate of 50 per second at 25° C. For the determination of η_l , 1 ml of the pourable liquid vehicle is placed onto the plate of a Haake RS 150 rheometer. The temperature is controlled in the range of typical room temperature, about 25° C. A cover is used on the measuring system and a solvent-saturated atmosphere provided to prevent evaporation of water, ethanol, or other volatile components from the sample during the test. A 35 mm diameter parallel plate measuring system is lowered onto the sample, leaving a gap of about 1 millimeter, and an equilibration shearing of approximately 10 per second is applied for 10 seconds. Then, a constant shearing rate of 50 per second is applied for 30 seconds. The viscosity η_l is read from the instrument at the 30 second time point.

For the determination of η_g , two dilutions of the pourable liquid vehicle are made with water. The first dilution is made to contain 75% by weight of the pourable liquid vehicle, and 25% by weight of additional water. The second dilution is made to contain 50% by weight of pourable liquid vehicle and 50% by weight of additional water. The pourable liquid vehicle and water are combined in a vial and a tight seal applied to prevent evaporation of components. The vial contents are mixed in an unusual manner, by repeated centrifugation. This is necessary since some of the combinations are very viscous gels. Specifically, the vials are centrifuged (using for example a Beckman GS-6R centrifuge, available from Beckman Instruments, Palo Alto, Calif.) 20 minutes at 3000 RPM and 25° C. for at least four separate centrifuge runs. After each run the vials are inverted. Additional runs are conducted in the centrifuge to ensure complete mixing. 1 ml of the gelled sample is then loaded onto the plate of the same rheometer used for the measurement of η_g , except that the temperature is controlled at the normal body temperature of a human, 37° C. An identical rheometer measurement program is used as for determination of η_g . The triggered viscosity factor for both the 25% and 50% dilution of the sample is calculated from η_g and η_g as described by the formula above. These two dilutions have been found to be useful for measuring the gelling functionality of the pourable liquid vehicles of the invention in a standardize method, because some of the pourable liquid vehicles may require a greater or lesser amount of water in order to trigger the gelling character. The use of other water dilutions for determination of η_g , ranging from about 5% up to about 70%, would also be expected to provide a demonstration of the unique, gelling character of the invention, but the dilution which yields a maximal value of T varies depending upon the exact pourable liquid vehicle being tested.

All percentages of the components comprising the invention are herein referred to their weight in the pourable liquid vehicle as a whole.

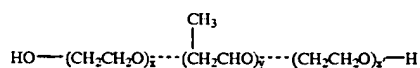
The present invention is a pourable liquid vehicle comprising:

- (a) from about 26% to about 100% polyoxyalkylene block copolymer;
- (b) from about 0% to about 70% glycol; and
- (c) from about 0% to about 50% water;

wherein said vehicle is used to deliver compositions, materials and substances to moistened surfaces and aqueous environments said vehicle has a viscosity value η_g less than or equal to 7 pascal-seconds and the value T greater than or equal to about 1.3.

Polyoxyalkylene Block Copolymer

Polyoxyalkylene block copolymers herein referred to as "poloxamers" are nonionic block copolymers of ethylene oxide and propylene oxide corresponding to the following structure:



wherein x, y, and x' have a value wherein the pourable liquid vehicle has a viscosity value η_g less than or equal to 7 pascal-seconds and the value T greater than or equal to about 1.3. Preferable polyoxyalkylene block copolymers useful in the present invention include wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, wherein the average molecular weight of said copolymer is from about 3000 to

about 15,000. More preferred is wherein x equals 37, y equals 58, and x' equals 37, and the copolymer has an average molecular weight of about 6500. Most preferred is wherein x equals 100, y equals 70, and x' equals 100, and the copolymer has an average molecular weight of about 12,600.

The poly(oxyethylene) segment is hydrophilic and the poly(oxypropylene) segment is hydrophobic. The level of the poloxamers useful in the present invention ranges from about 26% to about 100%, preferably from about 27.8% to about 95%, more preferably 30% to about 90% by weight of the pourable liquid vehicle. In other words, providing the poloxamer has the critical viscosities above, it can be used itself or when combined with other compositions, materials and substances.

A family of poloxamers are available and vary in the number of blocks, the overall average molecular weight, and in the percentage of the molecule which is hydrophilic. A block refers to a single polyoxyethylene or polyoxypropylene segment. Di-block and tri-block polymers have been described. In the case of tri-block copolymers, the blocks can be arranged in the format of one polyoxypropylene block surrounded by 2 polyoxyethylene blocks, that being the most common poloxamer structure, or alternatively as one polyoxyethylene block surrounded by 2 polyoxypropylene blocks, the latter sometimes referred to as a reverse poloxamer. Poloxamers are available under the trade names of Lutrol, Monolan, or Pluronic. The chemical structure, synthesis, and properties have been described [(poly(ethylene oxide)/poly(propylene oxide)) block copolymer surfactants, Paschalis Alexandridis, *Current Opinions in Colloid and Interface Science*, Vol 2, pp. 478-489 (1997) herein incorporated by reference.

For applications in the health care area, compositions embodying the present invention utilize a specific group of pharmaceutically acceptable block copolymers or poloxamers. These poloxamers are selected from the group consisting of Pluronic F127, P105, F108 and mixtures thereof, all available from BASF Corp.

Glycols

In addition to the poloxamers, it is desirable in some of the pourable liquid vehicles of the present invention to combine glycols with the poloxamers for controlling the viscosity of the pourable liquid vehicles. These glycols permit the pourable liquid vehicle to remain pourable while containing very high levels of the poloxamer so that administration is convenient, or so that the composition can readily pass through the bore of a syringe or other dosing apparatus. Additionally, these glycols provide solvent capacity for pharmaceutical actives or other composition components. The level of glycols in the present invention is from 0% to about 70%, preferably from about 10% to about 70% and most preferably from about 7% to about 62% of the pourable liquid vehicle.

Glycols are low molecular weight polyols and are selected from the group consisting of monosaccharides such as glucose (dextrose), fructose (levulose); disaccharides such as sucrose, lactose, maltose, cellobiose and other sugars, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, ethanol, honey, mannitol, polyethylene glycol, glycerol and mixtures thereof. Preferred glycols are selected from the group consisting of ethanol, glycerol and propylene glycol, and mixtures thereof. Absolute ethanol is available from Aaper Alcohol & Chemical Co., Shelbyville, Ky.

Water

In addition to the poloxamers, and, or the glycol, it is desirable in some of the pourable liquid vehicles of the

present invention to include water. Water is useful at a level from 0% to about 50%, preferably about 1% to about 46%, most preferably from about 2% to about 41% of the pourable liquid vehicle.

Preferred Embodiments

Preferred embodiments of the present invention utilizing the combination of poloxamers, polyols and water include the following:

1. from about 26% to about 65% Pluronic F127, from about 22% to about 38% ethanol and from about 8% to about 45% water.
2. from about 52% to about 60% Pluronic F108, from about 20% to about 25% ethanol and from about 17% to about 27% water.
3. from about 25% to about 50% Pluronic P105, from about 45% to about 65% propylene glycol and from about 5% to about 20% water.
4. from about 37% to about 77% Pluronic P105, from about 12% to about 28% ethanol, and from about 10% to about 45% water.
5. from about 26% to about 49% Pluronic F127, from about 2% to about 12% ethanol, from about 30% to about 68% propylene glycol, and from about about 7% to about 40% water.

Materials to be Delivered

As previously stated, the pourable liquid vehicles of the present invention are useful as delivery vehicles for desired compositions, materials and substances that may be dispersed into them. This could range from compositions, materials and substances that are desired to remain on an applied surface for a period of time to deliver a benefit. Examples include antimicrobials for cleansing surfaces including sinks, toilets and shower tile; to body wounds; oral treatment of gingival and buccal tissues as well as teeth surfaces; agricultural uses including elimination of undesirable plants, animals, viruses, bacteria insects, and the like.

The present invention is particularly useful for the delivery of health care compositions, materials, and substances. These materials can range from dietary compositions to promote nutrition or weight loss to pharmacologically effective amounts of agents selected from the group consisting of antibacterial substances, antihistamines, antitussives, anti-inflammatories, expectorants/mucolytics, mast cell stabilizers, leukotriene antagonists, methylxanthines, antioxidants, steroids, bronchodilators, antivirals, biologics, analgesics, anesthetics, antiarthritics, antiasthmatics, urinary tract disinfectives, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, muscle relaxants, antiprotozoals, and mixtures thereof.

Preferred embodiment of the present invention relates to compositions including pharmaceutically acceptable polyoxyalkylene block copolymer and glycols in combination with a pharmacologically active agent. Suitable classes of agents that can be administered by embodiments of the present invention include:

Antibacterial substances such as β -lactam antibiotics, such as cefoxitin, n-formamidoyl thienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, gramcidin, bacitracin, sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acids and analogs such as norfloxacin and the antimicrobial combination of fluoroalanine/pentizidone; nitrofurazones, and mixtures thereof.

Antihistamines, including, Hydroxyzine, Pyrilamine, Phenindamine, Dexchlorpheniramine, Clemastine

Diphenhydramine, Azelastine, Acrivastine, Levocabastine, Mequitazine, Astemizole, Ebastine, Loratadine, Cetirizine, Terfenadine, Promethazine, Dimenhydrinate, Meclizine, Tripeleminamine, Carbinoxamine, Cyproheptadine, Azatadine, Brompheniramine, Triprolidine, Cyclizine, Thonzylamine, Pheniramine, and mixtures thereof.

Antitussives, including, Hydrocodone, Noscapine, Benzonatate, Diphenhydramine, Chlophedianol, Clobutinol, Fominoben, Glauicine, Pholcodine, Zipeprol, Hydromorphone, Carbetapentane, Caramiphen, Levopropoxyphene, Codeine, Dextromethorphan, and mixtures thereof.

Antiinflammatories preferably Non-Steroidal Antiinflammatories (NSAIDS) including, Ketoprofen, Indoprofen, Indomethacin, Sulindac, Diflunisal, Ketorolac, Piroxicam, Meclofenamate, Benzydamine, Carprofen, Diclofenac, Etodolac, Fenbufen, Fenoprofen, Flurbiprofen, Mefenamic, Nabumetone, Phenylbutazone, Piroprofen, Tolmetin, Ibuprofen, Naproxen, Sodium naproxen, Aspirin, and mixtures thereof.

Expectorants/Mucolytics, including, Ambroxol, Bromhexine, Terpin, Guaifenesin, Potassium iodide, N-Acetylcysteine, and mixtures thereof.

Mast Cell Stabilizers, preferably intranasally, or orally administered mast cell stabilizers, including, Cromolyn, Oxatamide, Ketotifen, Lodoxamide, Nedocromil, and mixtures thereof.

Leukotriene Antagonists, including, Zileuton and others.

Methylxanthines, including, Caffeine, Theophylline, Enprofylline, Pentoxifylline, Aminophylline, Dyphylline, and mixtures thereof.

Antioxidants or radical inhibitors, including, Ascorbic acid, Tocopherol, Pycnogenol, and mixtures thereof.

Steroids, preferably intranasally administered steroids, including, Beclomethasone, Fluticasone, Budesonide, Mometasone, Triamcinolone, Dexamethasone, Flunisolide, Prednisone, Hydrocortisone and mixtures thereof.

Bronchodilators, preferably for inhalation, including, Albuterol, Epinephrine, Ephedrine, Metaproterenol, Terbutaline, Isoetharine, Terbutaline, Isoetharine, Pirbuterol, Biotolerol, Fenoterol, Rimiterol, Ipratropium, and mixtures thereof.

Antivirals, including, Amantadine, Rimantadine, Enviroxime, Nonoxinol, Acyclovir, Alpha-Interferon, Beta-Interferon, and mixtures thereof.

Biologics, including, cytokine and celladhesion molecule inhibitors, ICAM antagonists, interleukin agonists or antagonists, hormones, polypeptides, amino acids, nucleotides, antibodies, and mixtures thereof.

Analgesics such as aspirin, acetaminophen, diflunisal, and mixtures thereof. Anesthetics such as lidocaine, procaine, benzocaine, xylocaine, and mixtures thereof.

Antiarthritics such as phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone, probenecid, and mixtures thereof.

Antiasthma drugs such as theophylline, ephedrine, beclomethasone dipropionate, epinephrine, and mixtures thereof.

Urinary tract disinfectives such as sulfamethoxazole, trimethoprim, nitrofurantoin, norfloxacin, and mixtures thereof.

Anticoagulants such as heparin, bishydroxycoumarin, warfarin, and mixtures thereof.

Anticonvulsants such as diphenylhydantoin, diazepam, and mixtures thereof.

Antidepressants such as amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine, doxepin, and mixtures thereof.

Antidiabetics such as insulin, tolbutamide, tolazamide, acetohexamide, chlorpropamide, and mixtures thereof.

Antineoplastics such as adriamycin, fluorouracil, methotrexate, asparaginase, and mixtures thereof.

Antipsychotics such as prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, triflupromazine, and mixtures thereof.

Antihypertensive such as spironolactone, methyl dopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride, reserpine, and mixtures thereof.

Muscle relaxants such as melphalan, dantrolene, cyclobenzaprine, methocarbamol, diazepam, and mixtures thereof.

Antiprotozoals such as chloramphenicol, chloroquine, trimethoprim, sulfamethoxazole, and mixtures thereof.

For treatment of vaginal and urethral conditions requiring antifungal, amoebicidal, trichomonocidal agents or antiprotozoals, the following agents can be used: polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfanilamide, candicidin, sulfoxazole, nystatin, clotrimazole, metronidazole and mixtures thereof; antiprotozoals such as chloramphenicol, chloroquine, trimethoprim, sulfamethoxazole and mixtures thereof; antiviral effective compounds such as acyclovir and interferon. Spermicidal can be used such as nonoxynal.

EXAMPLES

Example I

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	1.47
Vehicle ¹	98.18
Sodium Saccharin	0.3
Monoammonium Glycyrizinate	0.05
Flavors and Colors	Flavors and Colors

¹Vehicle contains (w/w %):

Pluronic F127	55.51%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	26.48%
Water	18.01%

Preparation

Add the dextromethorphan base, sodium saccharin, and monoammonium glycyrrizinate into a clean vessel. Add ethanol and then the poloxamer and water. Mix until clear and uniform.

Example II

Composition for the Treatment of Cough and Decongestion

Component	% (w/w)
Dextromethorphan Base	1.47
Chloropheniramine Maleate	0.26
Vehicle ¹	97.92
Sodium Saccharin	0.3

-continued

Component	% (w/w)
Monoammonium Glycyrizinate	0.05
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):

Pluronic F127	55.66%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	26.55%
Water	17.79%

Preparation

Mill and screen the menthol and tienzoocaine to reduce the product particle size. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycyrrizinate into a clean vessel. Add eucalyptus oil, ethanol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example III

Demulcent Composition for the Treatment of Sore Throat

Component	% (w/w)
Vehicle ¹	96.845
Menthol	1.00
Benzocaine	2.00
Eucalyptus Oil	0.005
Sodium Saccharin	0.10
Monoammonium Glycyrizinate	0.05
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):

Pluronic F108	56.79%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	21.69%
Water	21.52%

Preparation

Mill and screen the menthol and benzocaine to reduce the product particle size. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycyrrizinate into a clean vessel. Add eucalyptus oil, ethanol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example IV

Composition for the Rectal Delivery of Acetaminophen

Component	% (w/w)
Vehicle ¹	95.0
Acetaminophen	5.0

¹Vehicle contains (w/w %):

Pluronic P105	44.21%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Propylene Glycol	52.63%
Water	3.16%

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Preparation

Mill and screen the acetaminophen to reduce the particle size. Add the acetaminophen into a clean vessel. Add propylene glycol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example V

Composition for the Topical Delivery of an Analgesic

Component	% (w/w)
Vehicle ¹	98.0
Ketoprofen	2.0
Perfumes	As Desired

¹Vehicle contains (w/w %):
 Pluronic F127 56.12%
 (BASF Specialty Chemicals, Mount Olive, N.J.)
 Ethanol 30.61%
 Water 13.27%

Preparation

Screen the ketoprofen to reduce the particle size. Add the ketoprofen into a clean vessel. Add ethanol to the vessel. Subsequently add poloxamer and water to the vessel. Mix until uniform.

Example VI

Composition for the Topical Delivery of an Analgesic

Component	% (w/w)
Vehicle ¹	95.0
Ibuprofen	5.0
Perfumes	As Desired

¹Vehicle contains (w/w %):
 Pluronic P105 63.16%
 (BASF Specialty Chemicals, Mount Olive, N.J.)
 Ethanol 18.95%
 Water 17.89%

Preparation

Screen the ibuprofen to reduce the particle size. Add the ibuprofen into a clean vessel. Add ethanol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example VII

Composition for the Delivery of an Oral Antimicrobial

Component	% (w/w)
Vehicle ¹	98.57
Triclosan Monophosphate	0.28
Menthol	1.00
Sodium Saccharin	0.10
Monoammonium Glycerizinnate	0.05

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-continued

Component	% (w/w)
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):
 Pluronic F108 55.80%
 (BASF Specialty Chemicals, Mount Olive, N.J.)
 Ethanol 21.30%
 Water 22.90%

Preparation

Mill and screen the menthol and triclosan monophosphate to reduce particle size. Add the menthol, triclosan monophosphate, sodium saccharin, and monoammonium glycerizinnate into a clean vessel. Add propylene glycol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example VIII

Composition for the Intranasal Delivery of a Decongestant

Component	% (w/w)
Vehicle ¹	99.32
Oxymetazoline HCl	0.05
Tyloxapol	0.15
Dibasic Sodium Phosphate	0.04
Monobasic Potassium Phosphate	0.13
Benzalkonium Chloride	0.04
Chlorhexidine Gluconate	0.26
Disodium EDTA	0.01

¹Vehicle contains (w/w %):
 Pluronic F127 40.27%
 (BASF Specialty Chemicals, Mount Olive, N.J.)
 Ethanol 26.18%
 Water 33.55%

Preparation

Add the dibasic sodium phosphate, monobasic potassium phosphate, disodium EDTA, benzalkonium chloride and oxymetazoline HCl into a clean vessel. Add tyloxapol, chlorhexidine gluconate, and ethanol to the vessel. Subsequently add, the poloxamer and water to the vessel. Mix until uniform.

Example IX

Composition to Vaginally Deliver Hormonal Replacement Therapy

Component	% (w/w)
Vehicle ¹	99.99
Beta Estradiol	0.01
Perfumes	As desired

¹Vehicle contains (w/w %):
 Pluronic P105 45.00%
 (BASF Specialty Chemicals, Mount Olive, N.J.)
 Propylene glycol 48.00%
 Water 7.00%

Preparation

Add the beta estradiol and propylene glycol into a clean vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

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Example X

Composition for the Rectal Delivery of an
Antiemetic

Component	% (w/w)
Vehicle ¹	99.75
Promethazine HCl	0.25

¹Vehicle contains 100.0% (w/w %) Pluronic L62 (BASF Specialty Chemicals, Mount Olive, N.J.)

Preparation

Mill and screen the promethazine HCl to reduce particle size. Add the poloxamer and the Promethazine HCl into a clean vessel. Mix until uniform.

Example XI

Composition for the Rectal Delivery of an
Antiemetic

Component	% (w/w)
Vehicle ¹	98.75
Carbomer ²	1.00
Promethazine HCl	0.25

¹Vehicle contains 100.0% (w/w %) Pluronic L62 (BASF Specialty Chemicals, Mount Olive, N.J.)

²Carbopol 974 available from B. F. Goodrich Company, Brecksville, Ohio

Preparation

Mill the promethazine HCl to reduce particle size. Sieve the carbomer and promethazine HCl and add to a clean vessel. Add the poloxamer. Mix until uniform.

Example XII

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40
Monoammonium Glycyrizinate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

Pluronic F127	33.56%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.51%
Water	13.42%
Propylene glycol	42.51%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dex-

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tromethorphan base and monoammonium glycerizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

⁵ Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

¹⁰ The preparation has a viscosity (η_p) of 0.67 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 10.5.

Example XIII

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40
Monoammonium Glycyrizinate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

Pluronic F127	29.08%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.51%
Water	24.61%
Propylene glycol	35.80%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glycerizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

⁴⁵ Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

The preparation has a viscosity (η_p) of 0.97 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 4.95.

Example XIV

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40

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-continued

Component	% (w/w)
Monoammonium Glycerizinnate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

Pluronic F127	40.27%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.51%
Water	13.42%
Propylene glycol	35.80%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glycerizinnate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

The preparation has a viscosity (η_p) of 2.14 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 6.05.

Example XV

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	97.8
Flavors	As desired

¹Vehicle contains (w/w %):

Pluraflo 1220	40.90%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.22%
Propylene Glycol	46.83%
Anhydrous glycerine	2.05

Preparation

Weigh the dextromethorphan into a clean vessel, add the ethanol and begin mixing. Add propylene glycol and mix until uniform and clear. Add Pluraflo and mix. Add glycerin and mix until uniform. Subsequently, add desired flavor component and mix until uniform.

The proportions of poloxamer:glycol in the preparation is 40.90:59.10.

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Example XVI

Composition for the Treatment of Otitis

Component	% (w/w)
ofloxacin	0.30
Vehicle ¹	98.95
Perfume	0.75

¹Vehicle contains (w/w %):

Pluraflo 1220	45.48%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	5.05%
Propylene Glycol	41.23%
Anhydrous glycerine	8.24

Preparation

Add propylene glycol, Pluraflo, glycerine and ethanol to a clean vessel. While stirring, add ofloxacin. Stir until a clear solution is obtained. Subsequently, add perfume and mix until uniform.

Example XVII

Composition for the Treatment of Glaucoma

Component	% (w/w)
Timolol maleate	0.25
Vehicle ¹	99.75

¹Vehicle contains (w/w %):

Pluraflo 1220	92.73%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	2.11%
Anhydrous glycerine	5.16

Preparation

Add glycerine, ethanol and Pluraflo to a clean vessel. Add Timolol. Cover tightly and stir until a clear solution is obtained.

Example XIII

Composition for the Treatment of Ulcers

Component	% (w/w)
Omeprazole (Free Base)	2.00
Vehicle ¹	95.89
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.25
Monoammonium Glycerizinnate	0.11
Acesulfame	0.35
Flavor	1.20

¹Vehicle contains (w/w %):

Pluronic F127	34.07%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.43%
Water	13.32%
Propylene glycol	42.18%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate

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to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, omeprazole base and monoammonium glycerizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

Example XIX

Composition for the Controlled Release of an Appetite Suppressant

Component	% (w/w)
Phenylpropanolamine Vehicle ¹	3.3
Sodium Metabisulfite	96.5
Disodium EDTA	0.10

¹Vehicle contains (w/w %):

Pluraflo 1220	70.12%
Propylene glycol	11.27
Ethanol	2.26%
Anhydrous glycerine	16.35

Preparation

Add alcohol, propylene glycol, EDTA, sodium metabisulfite and phenylpropanolamine to a clean vessel and begin mixing. Subsequently, add, Pluraflo and glycerine to the vessel. Mix until uniform.

This liquid may be filled into hard gelatin capsules that are then banded to prevent leakage, or it may be used as the fill for a soft elastic gelatin capsule. One capsule is made to contain 0.75 ml of the liquid, and taken 3 times daily provides controlled release of the phenylpropanolamine active. After swallowing, the gelatin shell dissolves in the gastrointestinal tract and the liquid fill immediately transforms in to a slow dissolving gel that provides controlled release of the phenylpropanolamine.

Example XX

Composition for the Injection of an Analgesic

Component	% (w/w)
Morphine Sulfate Vehicle ¹	1.0
	99.0

¹Vehicle contains (w/w %):

Pluraflo 1220	52.63%
Propylene glycol	35.79%
Ethanol	3.16%
Anhydrous glycerine	8.42%

Preparation

Add propylene glycol, ethanol, glycerine and morphine sulfate into a clean vessel and begin mixing. Subsequently, add poloxamer (Pluraflo) and mix until uniform.

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The composition provides pain relief when 1 mL is injected intramuscularly.

What is claimed is:

1. A pourable liquid vehicle comprising:

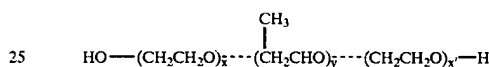
(a) from about 26% to about 97% by weight of a polyoxyalkylene block copolymer;

(b) from about 2% to about 70% by weight of a glycol; and

(c) from about 1% to about 50% by weight of water;

wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, wherein said vehicle has a viscosity value η_f less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3, and wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the glycol of from about 1:0.16 to about 1:2.20, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the glycol to the water of from about 1:0.08 to about 1:4.25.

2. The pourable liquid vehicle according to claim 1 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3,000 to about 15,000.

3. The vehicle according to claim 2 comprising from about 27.8% to about 95% of the polyoxyalkylene block copolymer wherein said vehicle has a viscosity η_f less than or equal to 2 pascal-seconds and value T is greater than or equal to about 2.

4. The vehicle according to claim 2 comprising from about 30% to about 90% of the polyoxyalkylene block copolymer wherein said vehicle has a viscosity η_f less than or equal to 2 pascal-seconds and value T is greater than or equal to about 5.

5. The vehicle according to claim 1 comprising from about 10% to about 70% by weight of the glycol.

6. The vehicle according to claim 5 wherein said glycol is selected from the group consisting of monosaccharides, disaccharides, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, honey, mannitol, polyethylene glycol, glycerol, and mixtures thereof.

7. The vehicle according to claim 1 comprising from about 1% to about 46% by weight of water.

8. The vehicle according to claim 2 comprising:

(a) from about 26% to about 65% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;

(b) from about 22% to about 38% by weight of the glycol; and

(c) from about 8% to about 45% by weight of water.

9. The vehicle according to claim 2 comprising:

(a) from about 25% to about 50% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;

(b) from about 45% to about 65% by weight of the glycol; and

(c) from about 5% to about 20% by weight of water.

10. The vehicle according to claim 2 comprising:

(a) from about 52% to about 60% by weight of the polyoxyalkylene block copolymer wherein x is equal to 128, y is equal to 58, and x' is equal to 128, and the average molecular weight of the polyoxyalkylene block copolymer is about 14,600;

(b) from about 20% to about 25% by weight of the glycol; and

(c) from about 17% to about 27% by weight of water.

11. The vehicle according to claim 2 comprising:

(a) from about 37% to about 77% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;

(b) from about 12% to about 28% by weight of the glycol; and

(c) from about 10% to about 45% by weight of water.

12. The vehicle according to claim 2 comprising:

(a) from about 26% to about 49% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;

(b) from about 30% to about 68% by weight of the glycol;

(c) from about 2% to about 12 % by weight of ethanol; and

(d) from about 7% to about 40% by weight of water.

13. A method for delivery of pharmacologically active agents to mammals by administering the pourable liquid vehicle of claim 1 to a moistened site on or in said mammal wherein said vehicle has a viscosity η_r less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.4.

14. The vehicle according to claim 1 wherein said compositions, materials, and substances are dietary compositions, pharmacologically active agents, or antimicrobials.

15. The vehicle according to claim 9 wherein the glycol is propylene glycol.

16. The vehicle according to claim 12 wherein the glycol is propylene glycol.

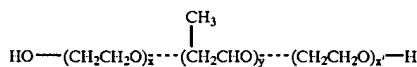
17. The vehicle according to claim 6 wherein the said vehicle further comprises from about 2% to about 70% by weight of ethanol, wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the ethanol of from about 1:0.16 to about 1:2.2, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the ethanol to the water of from about 1:0.08 to about 1:4.25.

18. A pourable liquid vehicle comprising:

(a) from about 26% to about 100% by weight of a polyoxyalkylene block copolymer; and

(b) from 0% to about 70% by weight of a glycol; wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, and wherein said vehicle has a viscosity value η_r less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3.

19. The pourable liquid vehicle according to claim 18 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3,000 to about 15,000.

20. The pourable liquid vehicle according to claim 18 wherein the glycol is selected from the group consisting of monosaccharides, disaccharides, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, honey, mannitol, polyethylene glycol, glycerol, and mixtures thereof.

21. The pourable liquid vehicle according to claim 20 wherein said vehicle further comprises from 0% to about 70% by weight of ethanol.

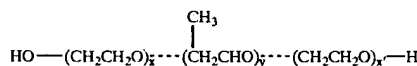
22. A pourable liquid vehicle comprising:

(a) from about 26% to about 97% by weight of a polyoxyalkylene block copolymer;

(b) from about 2% to about 70% by weight of ethanol; and

(c) from about 1% to about 50% by weight of water; wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, wherein said vehicle has a viscosity value η_r less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3, and wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the ethanol of from about 1:0.16 to about 1:2.2, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the ethanol to the water of from about 1:0.08 to about 1:4.25.

23. The pourable liquid vehicle according to claim 22 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3000 to about 15,000.

24. The vehicle according to claim 23 comprising:

(a) from about 26% to about 65% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;

(b) from about 22% to about 38% by weight of the ethanol; and

(c) from about 8% to about 45% by weight of water.

25. The vehicle according to claim 23 comprising:

(a) from about 52% to about 60% by weight of the polyoxyalkylene block copolymer wherein x is equal to 128, y is equal to 58, and x' is equal to 128, and the average molecular weight of the polyoxyalkylene block copolymer is about 14,600;

(b) from about 20% to about 25% by weight of the ethanol; and

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(c) from about 17% to about 27% by weight of water.

26. The vehicle according to claim 23 comprising:

(a) from about 37% to about 77% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;

(b) from about 12% to about 28% by weight of the ethanol; and

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(c) from about 10% to about 45% by weight of water.

27. A method for delivery of pharmacologically active agents to mammals by administering the pourable liquid vehicle of claim 22 to a moistened site on or in said mammal wherein said vehicle has a viscosity η , less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.4.

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US006316011B1

(12) **United States Patent**
Ron et al.

(10) **Patent No.:** **US 6,316,011 B1**
(45) Date of Patent: **Nov. 13, 2001**

(54) **END MODIFIED THERMAL RESPONSIVE HYDROGELS**

(75) Inventors: **Eyal S. Ron**, Lexington; **Lev Bromberg**; **Marina Temchenko**, both of Swampscott, all of MA (US)

(73) Assignee: **Madash, LLC**, Lexington, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/368,440**

(22) Filed: **Aug. 4, 1999**

Related U.S. Application Data

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(51) Int. Cl.⁷ **A61K 6/00**; **A61K 7/00**

(52) U.S. Cl. **424/401**; **424/78.02**; **424/78.03**; **424/78.18**

(58) Field of Search **424/400**, **401**, **424/78.02**, **78.03**, **78.08**, **78.19**, **78.18**, **78.31**, **40**, **443**, **450**, **489**, **59**

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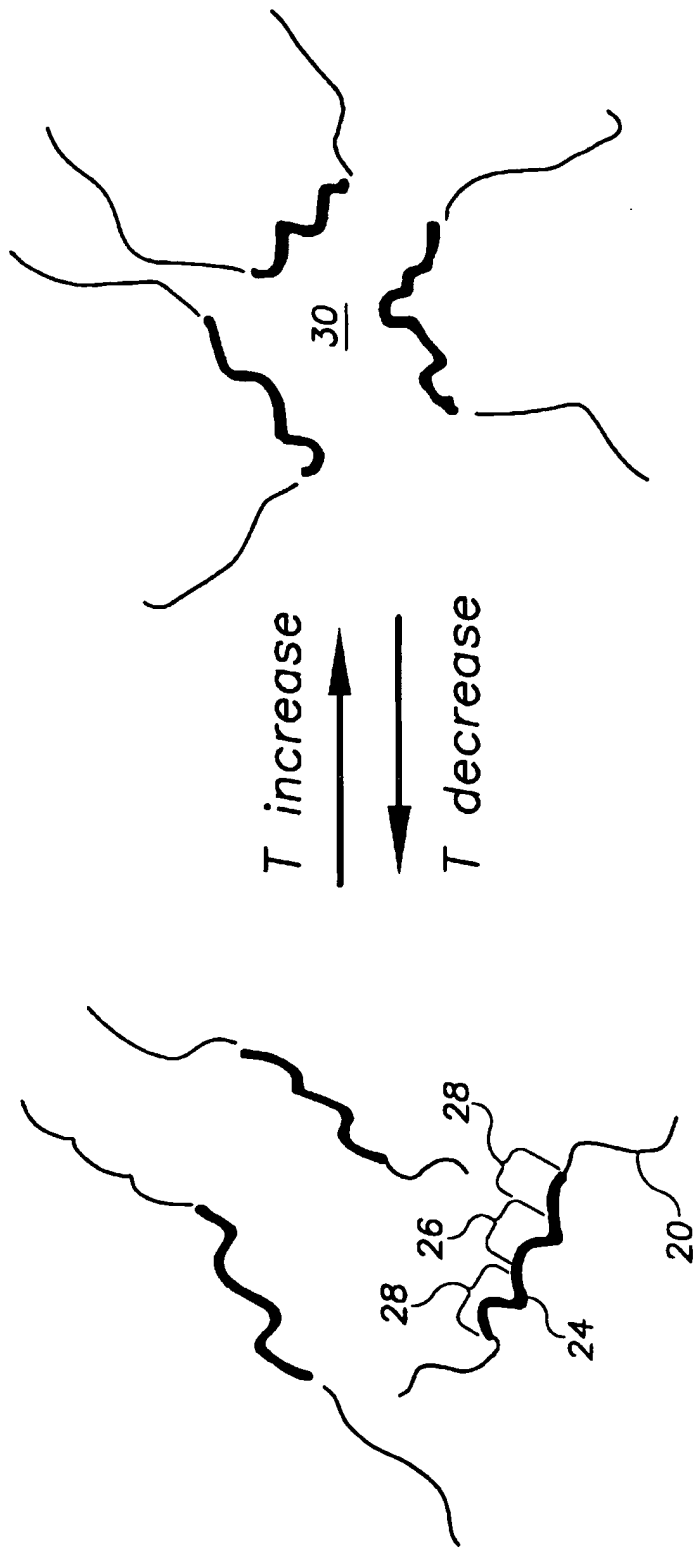
Primary Examiner—Dameron L. Jones

(57) **ABSTRACT**

A pharmaceutical composition includes a pharmaceutically acceptable carrier, comprising a reverse thermally viscifying polymer. The polymer includes a linear block copolymer, wherein at least one block comprises a poloxamer; and at least one block comprises a biocompatible polymer or oligomer, in an aqueous medium. The composition also includes an active agent which imparts a pharmaceutical or cosmetic effect. The composition viscosities in response to an environmental stimulus. The composition is suitable for administration of the pharmaceutical agent across dermal, otic, rectal, vaginal, ophthalmic, esophageal and nasal mucosal membranes.

41 Claims, 6 Drawing Sheets

FIG. 1



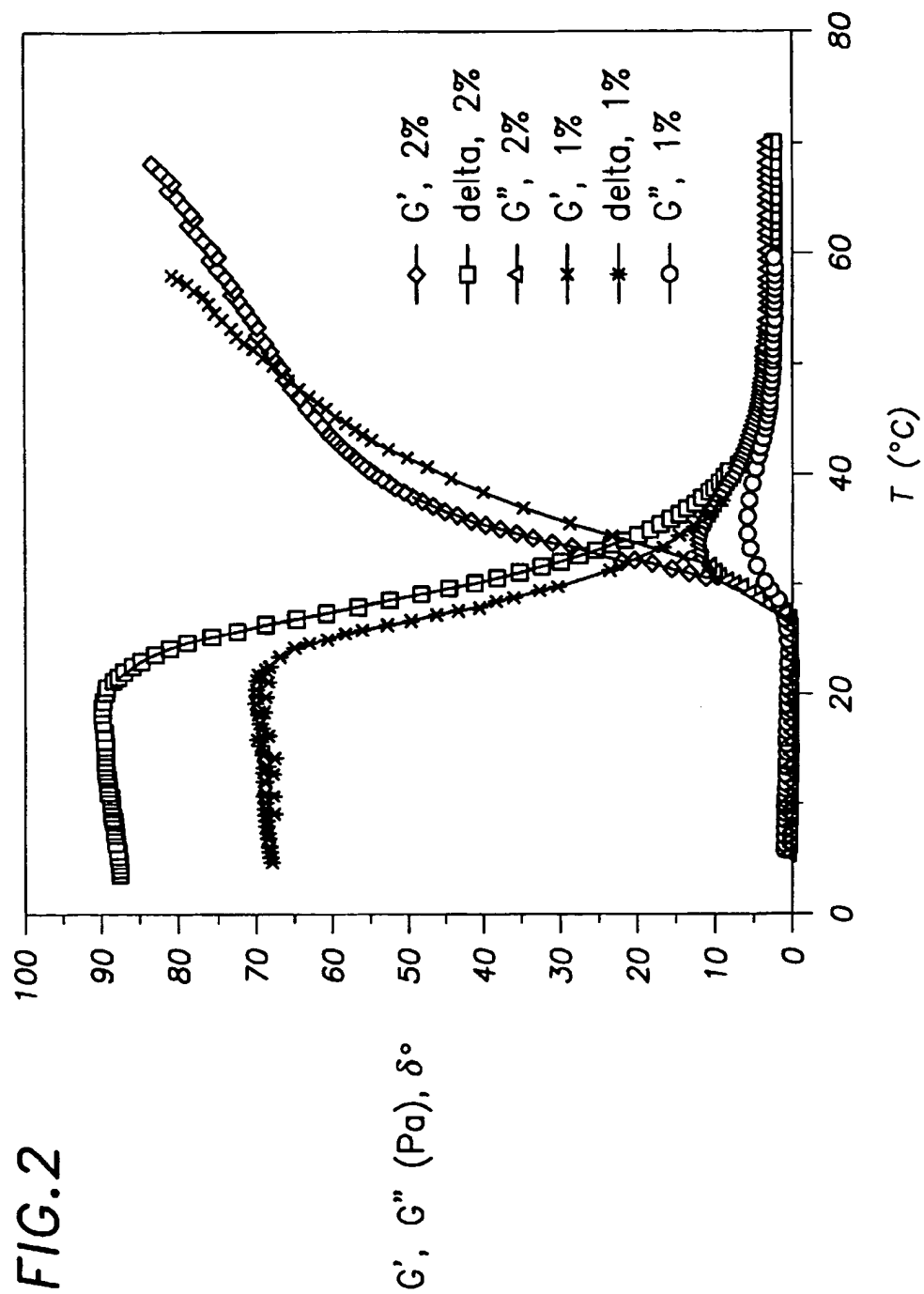


FIG. 3A

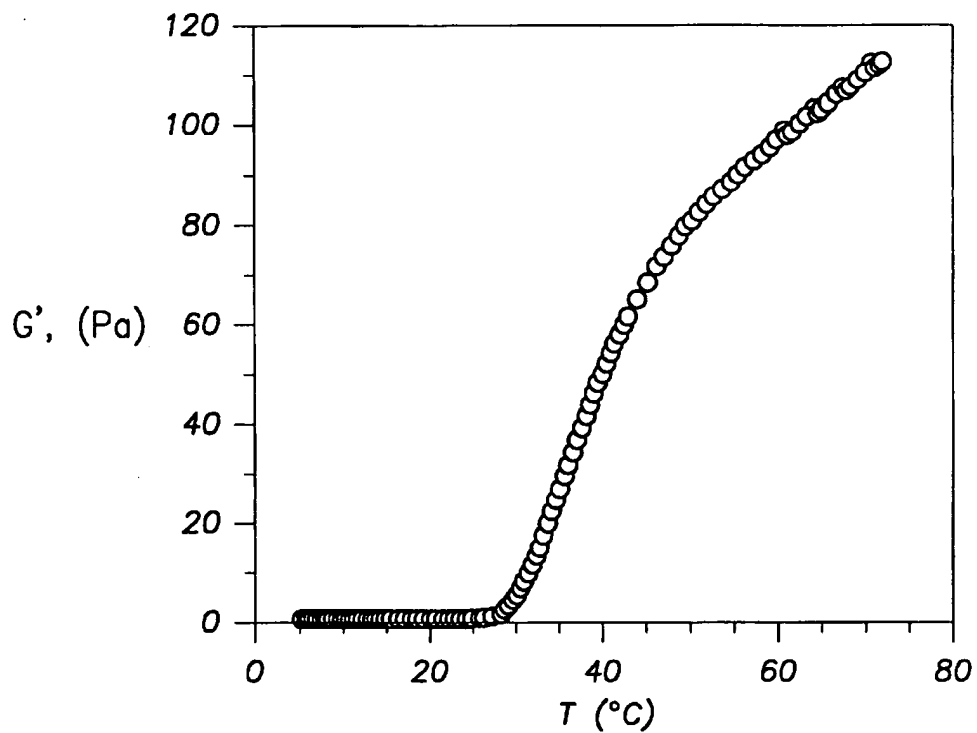
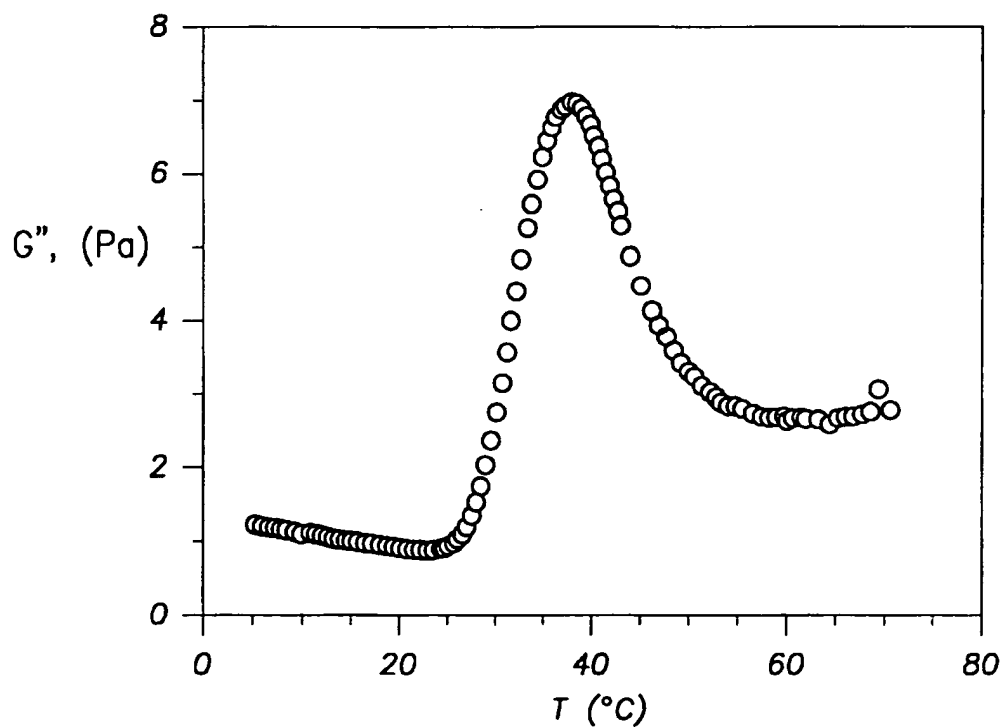
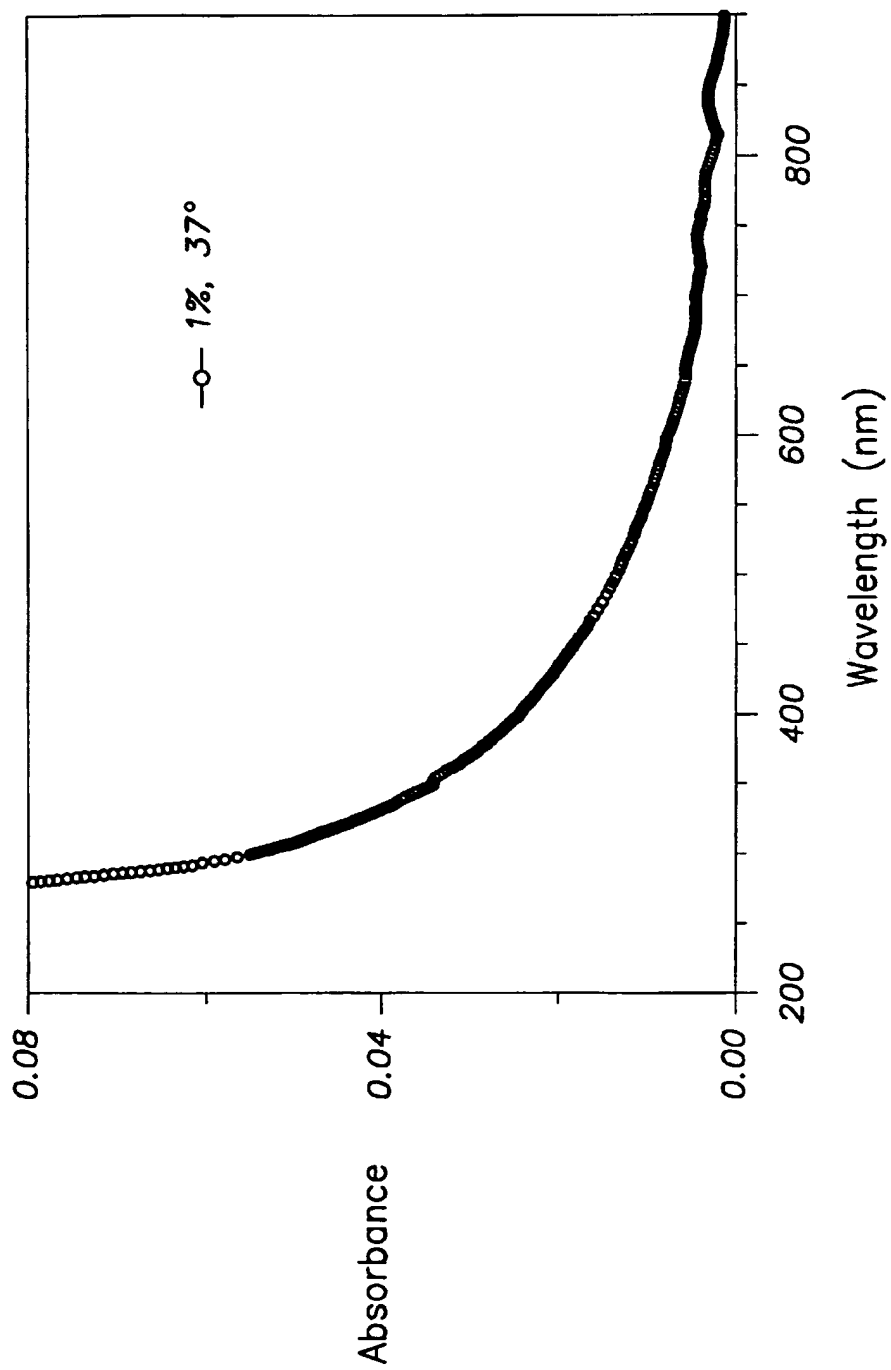


FIG. 3B





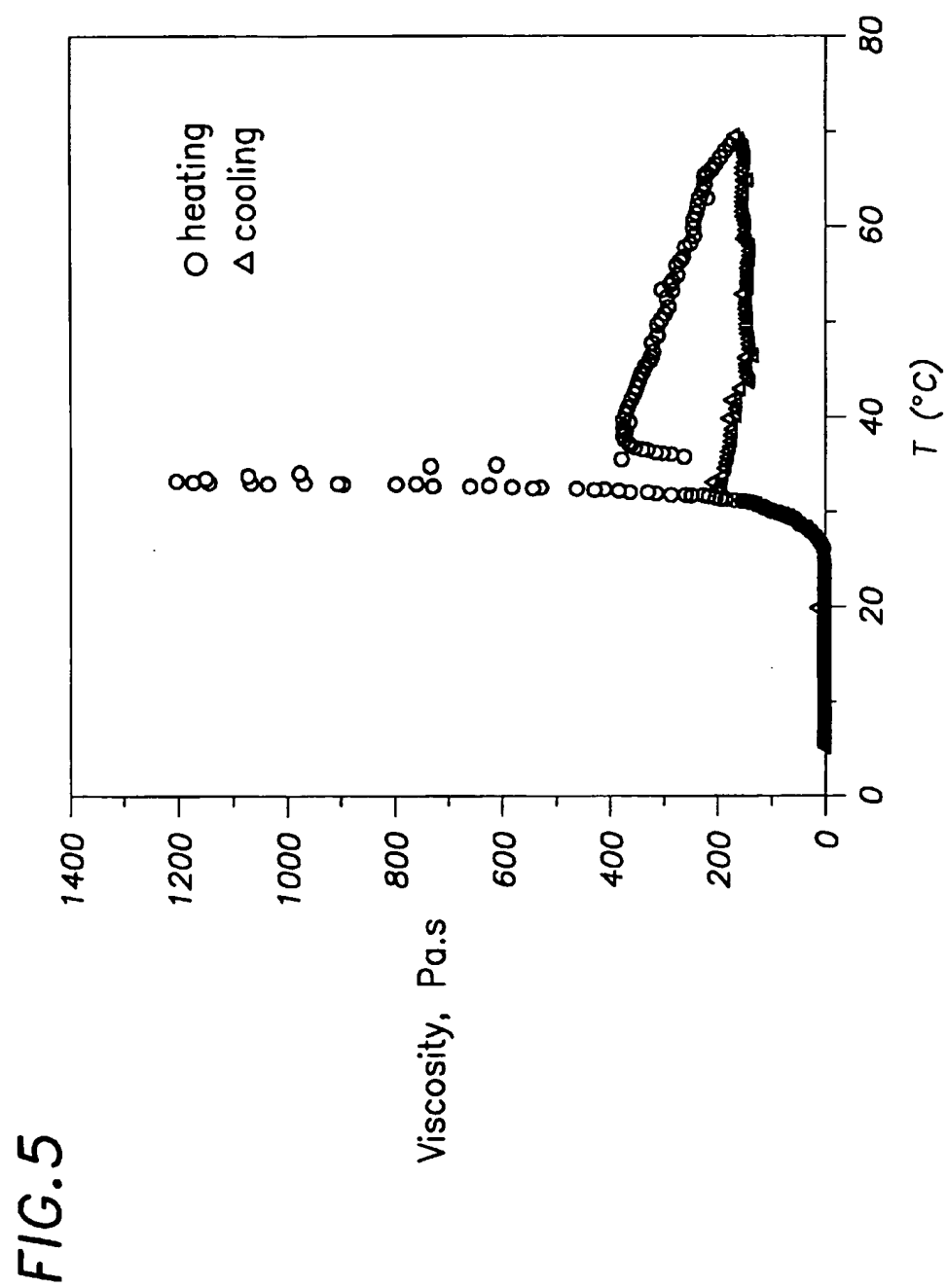
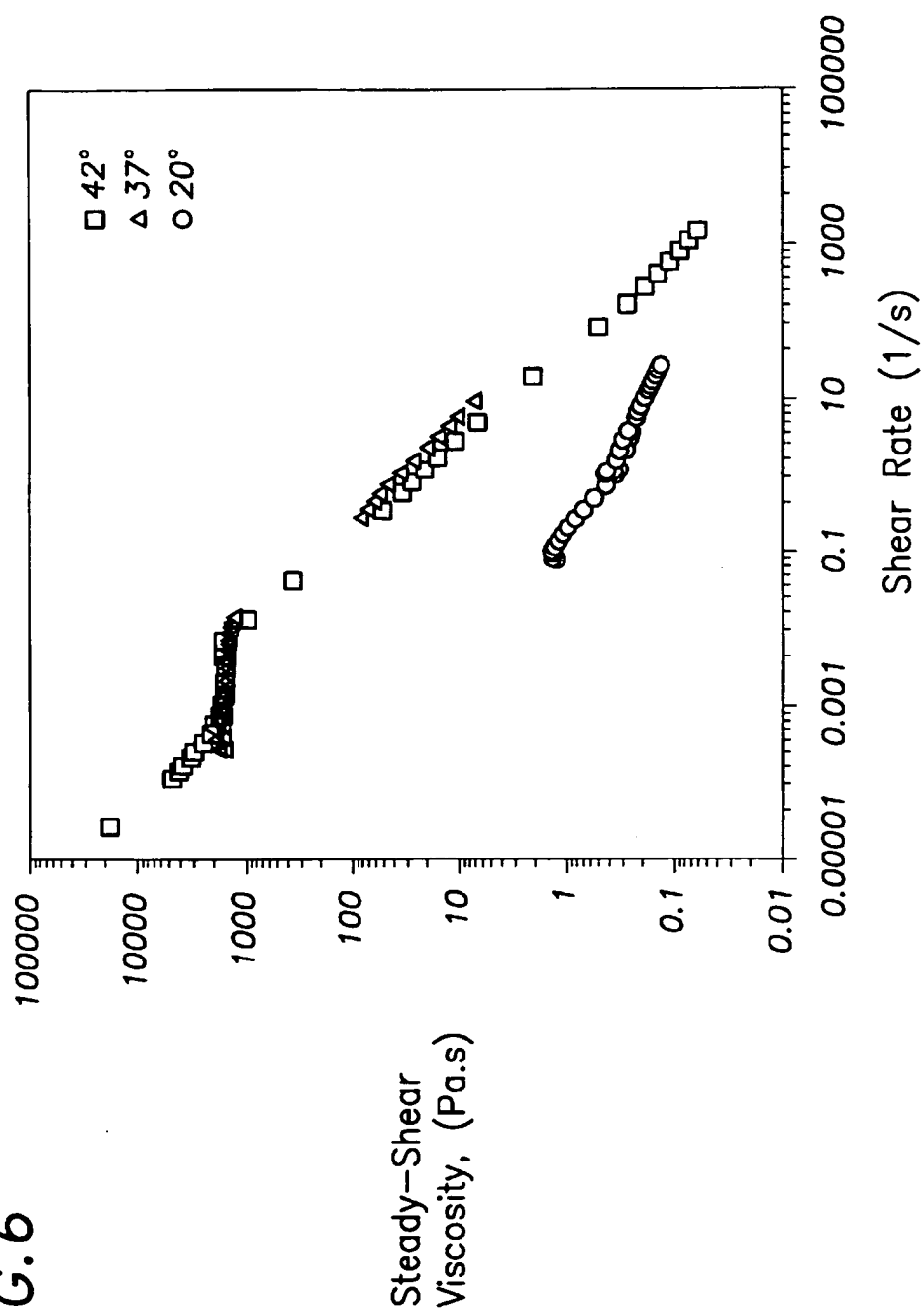


FIG. 6



END MODIFIED THERMAL RESPONSIVE HYDROGELS

This application is a continuation-in-part application U.S. Provisional Application No. 60/095,330 filed Aug. 4, 1998, entitled "Thermal Responsive and Bioadhesive Hydrogels" and of U.S. Provisional Application No. 60/097,741 filed Aug. 24, 1998, "Self-Assembling Copolymers and Methods Relating Thereto," which are hereby incorporated in its entirety by reference.

BACKGROUND OF THE INVENTION

The present invention relates to polymers and compositions useful in a variety of pharmaceutical and personal care products and applications, and in particular, compositions useful topical and/or mucosal applications, such as esophageal, otic, vaginal, rectal, ophthalmic and treatments of disorders and imperfections of the skin.

One of the major concerns in the delivery of drugs is the bioavailability of the drug. Depending upon the nature of the drug and the route of delivery, the bioavailability may be very low due to, for example, the degradation of oral-delivered drugs by hepato-gastrointestinal first-pass elimination or rapid clearance of the drug from the site of application. The net result is that frequent dosing may be required with higher than needed amounts of drug, which can lead to undesired side effects. Thus, it is desired by the pharmaceutical industry to have ways of administering drugs such that their availability can be controlled in an even dosing manner, the amounts of drugs can be kept as low as possible to minimize side effects, and dosing regime can be kept to a minimum to provide greater convenience to the subject, thus promoting greater compliance with appropriate dosing.

The mucosal tissue is an ideal site for drugs to be delivered locally and systemically because these tissues are exposed to an abundant blood supply. In addition, drug transport is aided by the fact that diffusion equilibria are not approached. Also, mucosal tissues have a very thin epithelium with minimal keratinized tissue that does not hinder the drug transport as compared to normal epidermal skin containing thick layers of keratinized tissues. Therefore, mucosal tissues offer an attractive surface to promote drug absorption.

Despite the advantages of mucosal tissue as a site for drug delivery, direct topical application of pharmacological agents onto mucosal tissues has very limited value, due to the facile clearance of those agents via washing or rubbing. The difficulty in the administration of such systems is the necessity for the drugs to remain in contact with the target tissue for a sufficient period of time to provide sufficient amount of drug to achieve the desired therapeutic effect. In addition to protection from pH, enzymatic attack and physiological removal by swallowing, the system needs to provide a long-term delivery to enhance the therapeutic profile (Guo, J-H; "Bioadhesive Polymer Buccal Patches for Buprenorphine Controlled Delivery: Formulation, In-vitro Adhesion and Release Properties", *Drug Dev. Ind. Pharm.*, 20(18), 2809, 1994; McQuinn, R. L.; et al; "Sustained Oral Mucosal Delivery in Human Volunteers of Buprenorphine from a Thin Non-eroding Mucoadhesive Polymeric Disc", *J. Control Rel.* 34, 243, 1995). Hence, specific formulations having improved bioadhesion designed to prolong the availability of the therapeutic product on the surface and to enable sustained release of the active ingredient are desired.

Bioadhesion or mucoadhesion is generally understood as the ability of a biological or synthetic material to "stick" to

mucous membrane, resulting in adherence of the material to the tissue for protracted period of time. This concept has received significant attention because of enhanced drug bioavailability due to the increased amount of time in which the bioadhesive dosage form is in contact with the targeted tissue, as compared to a standard dosage form. In order for the material to be bioadhesive, it must interact with mucous which is a highly hydrated, viscous anionic hydrogel layer protecting the mucosa.

Many instances are known in the pharmaceutical industry where it is desired to have certain properties of viscosity in order to facilitate the objectives noted above. Hydrogels, such as cellulose, have been included as thickeners in pharmaceutical compositions. A hydrogel is a polymer composition, in which the polymer forms a network swollen in water that is sufficiently stabilized either by covalent bonding or by physical bonding (hydrogen, ionic, hydrophobic, or van der Waals interactions). The hydrophilic areas of the polymer chain absorb water and form a gel region. The extent of gelation depends upon the volume of the solution which the gel region occupies.

Reversibly gelling solutions are known in which the solution viscosity increases and decreases with an increase and decrease in temperature, respectively. Such reversibly gelling systems are useful wherever it is desirable to handle a material in a fluid state, but performance is preferably in a gelled or more viscous state.

A known material with these properties is a thermal setting gel using poly(ethyleneoxide)/poly(propyleneoxide) block copolymers available commercially as Pluronic® poloxamers (BASF, Ludwigshafen, Germany) and generically known as poloxamers. See. U.S. Pat. Nos. 4,188,373, 4,478,822 and 4,474,751. Adjusting the temperature of the polymer gives the desired liquid-gel transition. However, concentrations of the poloxamer polymer of at least 18–20% by weight are needed to produce a composition which exhibits such a transition at commercially or physiologically useful temperatures. Also, solutions containing 18–20% by weight of responsive polymer are typically very viscous even in the "liquid" phase, so that these solutions can not function under conditions where low viscosity, free-flowing is required prior to transition. In addition, these polymer concentrations are so high that the material itself may cause unfavorable physiological interactions during use.

Another known system which is liquid at room temperature, but forms a semi-solid when warmed to about body temperature is formed from tetrafunctional block polymers of polyoxyethylene and polyoxypropylene condensed with ethylenediamine, commercially available as Tetronic® poloxamers. These compositions are formed from approximately 10% to 50% by weight of the poloxamer in an aqueous medium. See, U.S. Pat. No. 5,252,318. Although Pluronic®- and Tetronic®-based block copolymers exhibit reversible viscification, they did not offer any bioadhesion properties.

Various attempts have been made with limited success to combine the properties of a thermally gelling polymer and a bioadhesive polymer.

Himmelstein in U.S. Pat. No. 5,599,534 described the combination of a carboxylic acid-containing polymer such as poly(acrylic acid) with alkyl cellulose derivatives such as hydroxypropylmethylcellulose. Yet, the system required a pH shift in order to observe gelation.

Joshi et al. in U.S. Pat. No. 5,252,318 reports reversible gelling compositions which are made up of a physical blend of a pH-sensitive gelling polymer (such as a cross-linked

poly(acrylic acid) and a temperature-sensitive gelling polymer (such as methyl cellulose or block copolymers of poly(ethyleneoxide) and poly(propyleneoxide)). In compositions including methylcellulose, 5- to 8-fold increases in viscosity are observed upon a simultaneous change in temperature and pH for very low methylcellulose levels (1-4% by weight). See, FIGS. 1 and 2 of Joshi et al. In compositions including Pluronic® and Tetronic® poloxamers, significant increases in viscosity (5- to 8-fold) upon a simultaneous change in temperature and pH are observed only at much higher polymer levels. See, FIGS. 3-6 of Joshi et al.

Hoffman et al. in WO 95/24430 and D. Hourdet, F. L'aloret, A. Durand, F. Lafuma, R. Audebert, and J-P. Cotton, Small-Angle Neutron Scattering Study of Microphase Separation in Thermoassociative Copolymers, *Macromolecules*, 31(16): 5323-5335, 1998, incorporated herein by reference, disclose block and graft copolymers comprising a poly(acrylic acid) component and a temperature-sensitive polymer component. The block and graft copolymers are well-ordered and contain temperature- or salt-sensitive polymer grafts bonded to the poly(acrylic acid) backbone. The copolymers are described as having a lower critical solution temperature (LCST), at which both sol-gel transition and visible or microphase separation occur. Thus, the gelation is accompanied by the clouding and opacification of the solution. (Hourdet's polymers do not opacify). Light transmission is reduced, which may be undesirable in many applications, where the aesthetic characteristics of the composition are of some concern.

Bromberg et al. in "Responsive Polymer Networks and Methods of Their Use"(WO 97/00275); in "A novel family of thermogelling materials of poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) randomly grafted to poly(acrylic acid)," *J.Phys.Chem.B*, 102 (11):1956-1963 (1998); in "Self-assembly in aqueous solutions of polyether-modified poly(acrylic acid)," *Langmuir*, 14(20):5806-5812 (1998); and in "Properties of aqueous solutions and gels of poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)-g-poly(acrylic acid)," *J.Phys.Chem B*, 102 (52):10736-10744 (1998); incorporated herein by reference, describe a graft-comb copolymer system where the poly(acrylic acid) serves as a backbone and the poloxamer was attached to the backbone through their poly(propylene oxide) moieties. This hydrogel system has a reduced stability due to the initial oxidation of the Pluronic® polymer. Also, by hindering access to the poly(acrylic) backbone bioadhesivity of the system is reduced.

Thus, the known systems which exhibit reversible gelation are limited in that they require large solids content and/or in that the increase in viscosity less desired. In addition, some known systems exhibit an increase in viscosity which is accompanied with the undesirable opacification of the composite. Other systems do not exhibit the desired bioadhesion properties or the stability required for quality pharmaceutical products.

It is the object of the present invention to overcome these and other limitations of the prior art.

SUMMARY OF THE INVENTION

The present invention provides compositions which possess improved flow and gelation characteristics. The composition is composed of biocompatible building blocks and includes a component capable of reversible gelation or viscosification. The composition demonstrates excellent bioadhesion and is useful in drug delivery applications.

The composition comprises a linear block copolymer including a polyoxyalkylene, such as poloxamer, end-

modified by bioadhesive polymer, which may be poly(acrylic acid), or PAA, in an aqueous-based medium. The polymer is capable of aggregating in response to an increase in temperature.

In one aspect of the invention, the composition is capable of gelation or viscosification at very low solids content. In another aspect, the invention further provides compositions having a minimum solids content which are capable of sustained delivery of an active agent. The composition incorporates poloxamer:poly(acrylic acid) polymer as a carrier.

The present invention overcomes the limitations of the prior art by providing compositions that includes a linear block copolymer capable of bioadhesion and reversible gelation or viscosification upon exposure to the appropriate environmental stimulus.

The present invention further provides a composition for use in pharmaceutical or cosmetic formulations as a surfactant or emulsifier in the solubilization of additives and, in particular, hydrophobic additives, or as a stabilizer to provide stable emulsions at elevated temperatures, or as a suspension agent for otherwise insoluble additives.

New ways of delivering drugs at the right time, in a controlled manner, with minimal side effects, and greater efficacy per dose are continually sought by the drug delivery and pharmaceutical industries. The reversibly gelling polymer of this invention has the physico-chemical characteristics that make it a suitable delivery vehicle for conventional small chemical drugs as well as new macromolecular (e.g., peptides) drugs or therapeutic products. It is particularly well-suited for transmucosal delivery.

These and other aspects of the invention are described.

The reversibly gelling composition comprises a linear copolymer including a polyoxyalkylene component having a hydrophobic region and a hydrophilic region capable of aggregation in response to an environmental stimulus. The polyoxyalkylene is modified at each end by a polymer component to form a linear block copolymer. The polymer component is biocompatible and is selected to increase the molecular weight of the composition. The polymer component does not interfere with the aggregation properties of the polyoxyalkylene.

In a preferred embodiment of the invention, the polymer component possesses bioadhesive or mucoadhesive properties. In a particularly preferred embodiment of the invention, the polymer component includes a poly(vinylcarboxylic acid), such as poly(acrylic acid) and poly(methacrylic acid), and the like. In a preferred embodiment, the polyoxyalkylene comprises a poloxamer.

In another aspect of the invention, a pharmaceutical composition is provided which includes the reversibly gelling block copolymer of the invention and a pharmaceutical agent selected to provide a preselected pharmaceutical effect.

A pharmaceutical effect is one which seeks to treat the source or symptom of a disease or physical disorder. Pharmaceuticals include those products subject to regulation under the FDA pharmaceutical guidelines, as well as consumer products. In addition, the composition may include agents promote bodily attractiveness or masking the physical manifestations of a disorder or disease, in lieu or in addition to the treatment of a physical disorder. The same agent may have either a cosmetic or pharmaceutical effect, depending upon the amounts used and the manner of administration.

The block copolymer and pharmaceutical compositions of the invention exhibit many advantages. Due to the gelling effect at physiologically appropriate conditions, they pos-

sesses the appropriate thickness, emolliency and cosmetic effect with a minimum of solids content. Furthermore, as is described hereinbelow, the linear block copolymer composition may be useful as a suspending agent for otherwise insoluble additives. Additionally, the block copolymer and pharmaceutical compositions of the invention are capable of solubilizing emulsions at elevated temperatures.

In another aspect of the invention, the polyoxyalkylene:poly(acrylic acid) polymer is incorporated into a composition to stabilize and solubilize hydrophobic agents. The composition may be included to increase emulsion stability. Many emulsions, i.e., suspension of small droplets or particles of a first material in a second material, lose viscosity upon heating. The polyoxyalkylene:poly(acrylic acid) block copolymer composition retains its emulsifying properties even with temperature increase.

By "polyoxyalkylene" as that term is used herein, it is meant an oligomer or polymer of an oxyalkylene, or $-O(CH_2)_n-$, group, where n is in the range of 1 to 10 and where any H may be substituted for a linear or branched alkyl group. In preferred embodiments, n is 2 or 3, and is either unsubstituted or substituted by methyl group. The polyoxyalkylene component of the polymer possesses regions of hydrophobic character, e.g., poly(oxypropylene) blocks, and hydrophilic character, e.g., poly(oxyethylene) blocks in order to facilitate aggregation.

By "gelation" or "viscosification" as those terms are used herein, it is meant a drastic increase in the viscosity of the polymer solution. Gelation is dependent on the initial viscosity of the solution, but typically a viscosity increase at pH 7 and 1 wt % polymer concentration is in the range of preferably 2- to 100-fold, and preferably 5- to 50-fold, and more preferably 10- to 20-fold for a composition which is used in the preparation of the compositions of the invention. Such effects are observed in a simple polymeric solution and the effect may be modified by the presence of other components in the final composition.

By "reversibly gelling" as that term is used herein, it is meant that the process of gelation takes place upon an increase in temperature rather than a decrease in temperature. This is counter-intuitive, since solution viscosity typically decreases with an increase in temperature.

By "end-modified", as that term is used herein, it is meant that the polyoxyalkylene component is modified at its termini by chemical conversion and/or addition to the component. This in contrast to modifications which may occur along the backbone of the polyoxyalkylene.

By "use conditions" as that term is used herein it is meant all conditions to which the composition is likely to be exposed during its use, including during shipment and storage as well as during medical treatment or personal care.

The novel interaction between the constituent polymers components of the reversibly gelling composition permits formation of gels at very low solids content. Gelation and/or viscosification is observed in aqueous solutions having about 0.01 to 20 wt % of the polyoxyalkylene component and about 0.01 to 20 wt % of the end-modifying polymer component. A typical reversibly gelling composition may be comprised of about 0.01 wt % to about 1 to 8 wt %, preferably less than about 4 wt % of total polymer solids (e.g., polyoxyalkylene and biocompatible polymer), and more preferably less than 1 wt % total polymer solids, while still exhibiting reverse thermal viscosification. Of course, the total solids content of the composition, including additives and the pharmaceutical agent, may be much higher.

The relative proportion of polyoxyalkylene polymer and end-modifying polymer may vary in the composition,

dependent upon the desired properties of the composition. Exemplary polymer compositions range from about 1:10 to about 10:1 polyoxyalkylene polymer:bioadhesive polymer. In one embodiment, the polyoxyalkylene component is present in a range of about 1 to 20 wt % and the end-modifying polymer is present in a range about of 99 to 80 wt %. In another embodiment, the polyoxyalkylene polymer component is present in a range of about 21 to 40 wt % and the polymer component is present in a range of about 79 to 60 wt %. In another embodiment, the polyoxyalkylene polymer component is present in a range of about 41 to 50 wt % and the polymer component is present in a range of about 59 to 50 wt %. In another embodiment, the polyoxyalkylene polymer component is present in a range of about 51 to 60 wt % and the polymer component is present in a range of about 49 to 40 wt %. In yet another embodiment, the polyoxyalkylene polymer component is present in a range of about 61 to 90 wt % and the polymer component is present in a range of about 39 to 20 wt %. In another embodiment, the polyoxyalkylene polymer component is present in a range of about 81 to 99 wt % and the polymer component is present in a range of about 19 to 1 wt %. A 50:50 mixture of poloxamer and poly(acrylic acid) has been demonstrated to provide the desired thermoviscosifying effect under most circumstances.

The reversibly gelling polymer described above may be included in a composition as a delivery vehicle for an active agent. In addition, the reversibly gelling composition may be included to improve the flow characteristics, thickness and other properties of the composition.

In one aspect of the invention, the reversibly gelling composition is incorporated into a composition to impart thickening properties to the composition at the use and/or application temperature. Such thickening properties include enhanced overall viscosity, as well as a desirable viscosity response with temperature. The composition may be useful as a thickener in pH ranges where other thickeners are not effective.

In another aspect of the invention, the reversibly gelling composition is incorporated into a composition to stabilize and solubilize hydrophobic agents in the composition. The reversibly gelling composition may be included to increase emulsion stability. Many emulsions (a suspension of small droplets or particles of a first material in a second material) lose viscosity upon heating. The reversibly gelling composition retains its emulsifying properties even at elevated temperatures.

In addition, the reversibly gelling composition may be included in the composition to impart emolliency to the composition. The composition may also act as a film-forming agent after it has been applied to the skin or other mucosal membrane. This film-forming agent may be used as a barrier to prevent water loss from the skin which contributes to the moisturization of the skin. The formed-film could also provide protective coating ("band-aid") to protect the tissue against environmental challenge(s) or to provide a mechanical separation between to adjust tissues (adhesion prevention).

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BRIEF DESCRIPTION OF THE DRAWING

The invention is described with reference to the Drawing, which is presented for the purpose of illustration and is in no way intended to be limiting, and in which:

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FIG. 1 is a schematic illustration of the poloxamer:poly (acrylic acid) polymer below and above the transition temperature illustrating the aggregation of the hydrophobic poloxamer regions;

FIG. 2 is a graph of G' , G'' and δ° vs. temperature for a 1 wt % and 2 wt % of a poloxamer/poly(acrylic acid) (1:1) aqueous composition;

FIG. 3 is a graph of G' vs. temperature (3A) and G'' vs. temperature (3B) for a 2 wt % poloxamer/poly(acrylic acid) (1:1) aqueous composition demonstrating reversibility of the viscosity response;

FIG. 4 is a electronic spectrum of a 1 wt % poloxamer/poly(acrylic acid) (1:1) aqueous composition indicating translucence in the visible range;

FIG. 5 is a graph of viscosity vs. temperature for a 2 wt % poloxamer/poly(acrylic acid) (1:1) aqueous composition; and

FIG. 6 is graph of steady state viscosity vs. shear rate for an 8 wt % poloxamer/poly(acrylic acid) (1:1) aqueous composition at various temperatures.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a composition comprising a polyoxyalkylene component that is end-modified with a biocompatible polymer to provide a linear copolymer. The polyoxyalkylene may be a thermogelling polymers, such as Pluronic® (BASF, Ludwigshafen, Germany) capped by both ends by oligomer of a mucoadhesive or bioadhesive polymer. The end-modified polyoxyalkylene compositions of the invention exhibit a reversible gelation at body temperature (25–40° C.) and/or at physiological pH (ca. pH 3.0–9.0) and even in basic environments up to pH 13 (e.g., the gastro-intestinal environment) are particularly preferred for pharmaceutical and personal care applications. The end-modified polyoxyalkylene polymer functions as an environmentally sensitive thickening agent, and in addition possesses surfactant and emulsifying capabilities which may be beneficial in a pharmaceutical or personal care composition.

End-modified polyoxyalkylene block copolymer solutions at appropriate pH exhibit flow properties of a liquid at about room temperature, yet rapidly thickens into a gel consistency of at least about five times greater, preferably at least about 10 times greater, and even more preferably at least about 30 times and up to 100 times greater, viscosity upon increase in temperature of about 10 C. and preferably about 5 C. The reversibly gelling composition of the present invention exhibit gelation even at very low polymer concentrations.

The polyoxyalkylene component contains a hydrophilic region and a hydrophobic region which makes it able to change its degree of association and/or agglomeration in response to an environmental stimulus. The stimulus most commonly is temperature, pH, ionic concentration, or solvent concentration, but other stimuli are within the scope of the invention if they cause the poloxamer to aggregate. Temperature is a preferred environmental trigger. The aggregation may be in the form of micelle formation, precipitation, labile crosslinking or other factors.

Exemplary polyoxyalkylenes are block copolymers of polyoxyethylene and polyoxypropylene having the general formula of a triad ABA block copolymer, b(EO) a(PO)b(EO) a, where EO=ethylene oxide and PO=propylene oxide moieties. Pluronic® (BASF) triblock polymers are commercially available for a in the range of 6 to 140 and b ranging from 6–100. Preferred embodiments include Pluronic® (BASF) triblock polymers for a in the range of 16 to 48 and b ranging from 54–62.

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Other exemplary polyoxyalkylene polymers include alkyl poloxamers, which are a product of alcohol condensation reactions with a terminal alkyl or arylalkyl group. The alkyl group should have hydrophobic character, such as butyl, hexyl and the like. An alkyl poloxamer may have the general formula $R-(OCH_2CH)_nOH$, where R is a nonpolar pendant group such as alkyl and arylalkyl and the like, and n is in the range of 5–1000. A preferred alkylpoloxamer is polyethylene glycol mono(nonylphenyl)ether.

One or more polyoxyalkylene components may be used in the reversibly gelling composition of the present invention. In still other embodiments, the polyoxyalkylene component may additionally include cellulosic, cellulose ethers and guar gums which possess hydrophobic and hydrophilic regions along the polymer backbone which permit aggregation behavior.

The end-modification is achieved by oligomers or polymers which serves as an extension for the polyoxyalkylene poloxamer so that a multi-component composition is formed. This results in an extended linear polymer. The end-modifying polymer component increases the molecular weight of the composition, which amplifies the viscosification response. In addition, the polymer component may be a bioadhesive or mucoadhesive.

Suitable end-modifiers components include ionizable polymers. The ionizable polymers of the present invention include linear, branched and/or crosslinked polymers. Of particular interest are carboxyvinyl polymers of monomers such as acrylic acid, methacrylic acid, ethacrylic acid, phenyl acrylic acid, pentenoic acid and the like. Poly(acrylic acid) and its salts is a preferred carboxyvinyl polymer. One or more poly(carboxyvinyl) polymers may be used in the polyoxyalkylene composition compositions of the present invention. Copolymers, such as by way of example only, copolymers of acrylic acid and methacrylic acid, are also contemplated.

Additional characteristics of the non-polyoxyalkylene component is its ability to provide mucosal adhesion. Bioadhesion or mucoadhesion is generally understood as the ability of a biological or synthetic material to "stick" to mucous membrane, resulting in adherence of the material to the tissue for protracted period of time. This concept has received a significant attention due to the potential applications in drug delivery and in enhanced drug bioavailability, which results from lengthening the period of time in which the bioadhesive dosage form is in contact with the targeted tissue versus standard dosage form. In order for the material to be bioadhesive, it must interact with mucus, which is highly hydrated, viscous anionic hydrogel layer protecting the mucosa. The mucin is composed largely of flexible glycoprotein chains, which are cross-linked. In order to obtain a bioadhesive system a few factors need to be analyzed carefully (Ahuja, A.; Khar, R. K.; Ai, J. Mucoadhesive Drug Delivery Systems", *Drug Dev. Ind. Pharm.* 23(5):489 (1997)) First, the bioadhesive material has to be of high molecular weight polymers. These polymers entangled into the mucin layer forming a complex layer of polymers and mucin. Second, the presence of functional groups on the polymeric backbone is important as well. It was observed that hydrogen bonding plays an important roll in adhesion (Mortazavi, S. A. "An in-vitro Assessment of Mucus Adhesive Interactions", *Intl. J. Pharm.*, 124(2):173

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(1995)). Third, the surface energy, that is, the degree of hydrophobicity, plays an important role. When a good match is found between the polymers and the mucin, a good adhesion occurs (Lehr, C. M., et. Al; "Oral Bioadhesive Drug Delivery Systems—Effects on GI Transit and Peptide Absorption", *Pharm. Res.*, 7(9), PDD 7226 (1990)). Finally, systems that swell in water will enhance the adhesion to the mucosa by dehydrating it and "pulling" the mucin chains into the delivery system.

Poly(acrylic acid) is a demonstrated bioadhesive polymer. It may be linear, branched and/or crosslinked. Poly(acrylic acid) is capable of ionization with a change in pH of the solution. By ionization, as that term is used with respect to poly(acrylic acid), it is meant the formation of the conjugate base of the acrylic acid, namely acrylate anion. As used herein, poly(acrylic acid) includes both ionized and non-ionized versions of the polymer. Changes in ionic strength may be accomplished by a change in pH or by a change in salt concentration. The viscosifying effect of the composition is partly a function of the ionization of the poly(acrylic acid); however, reverse thermal gelling may occur without ionization. Changes to the ionic state of the polymer causes the polymer to experience attractive (collapsing) or repulsive (expanding) forces. Where there is no need or desire for the composition to be applied in a high viscosity state, it may be possible to prepare the composition as non-ionized poly(acrylic acid). The body's natural buffering ability will adjust the pH of the applied composition to ionize the poly(acrylic acid) and thereby develop its characteristic viscosity.

Exemplary copolymers of the invention include:

$(\text{CH}_2\text{CHR})_n\text{—Q—}(\text{CH}_2\text{CH}_2\text{O})_x(\text{CH}_2\text{CH}(\text{CH}_3)\text{O})_y$, $(\text{CH}_2\text{CH}_2\text{O})_x\text{—Q—}(\text{CH}_2\text{CHR})_m$, whereby a poloxamer is connected, at its termini, with a vinyl moiety. Q is a linking moiety and, in a preferred embodiment, Q is C—C, C—O, C(O)—NH, S—C, C(O)—O functionality and the like. R is a carboxyl, and n, m, x and y, are independently selected and in the range of 1 and 1000, or

$(\text{CH}_2\text{CHR})_n\text{—Q—}(\text{CH}_2\text{CH}_2\text{O})_x(\text{CH}_2\text{CH}(\text{CH}_3)\text{O})_y$, $(\text{CH}_2\text{CH}_2\text{O})_x\text{—Q—}(\text{CH}_2\text{CHR})_n\text{—Q—}(\text{CH}_2\text{CH}_2\text{O})_x$, $(\text{CH}_2\text{CH}(\text{CH}_3)\text{O})_y(\text{CH}_2\text{CH}_2\text{O})_n\text{—Q—}(\text{CH}_2\text{CHR})_m$, in which alternating blocks of poloxamer and acrylic acid oligomers are joined. R and Q are as defined herein above. In preferred embodiments, a poloxamer is end-capped using acrylic acid oligomers with an ester linkage, or end-capped using acrylic acid oligomers with an ether linkage and R is COOH or COOCH₃.

Without intending to be bound by any particular mechanism or chemical structure, it is believed that the combination of biocompatible polymer component and the poloxamer component in a linear copolymer gives the composition its unique properties. Viscosity is a function of the molecular weight of the solubilized composition. Aggregation of the poloxamer component from a few molecules increases the effective molecular weight of the polymer network. The aggregation may be in the form of micelle formation, precipitation, labile crosslinking or other factors. The biocompatible polymer increases the molecular does not interfere with the poloxamer aggregation due to the linear block morphology of the polymer. The linear structure permits enhanced interaction of neighboring poloxamer units and maximizes access of the bioadhesive component to the site of administration.

The aggregation process may be understood as occurring as shown in FIG. 1, in which a polymer component 20 represents a biocompatible polymer, such as poly(acrylic

acid), and region 24 represents the poloxamer component of the linear copolymer. The poloxamer includes a hydrophobic poly(propyleneoxide) region 26 and a hydrophilic poly(ethyleneoxide) region 28. Below the transition temperature, no aggregation is observed. At or above the transition temperature, the poloxamer regions 24 associate to form aggregations or micelles 30. The association increases the effective molecular weight of the composition with the corresponding increase in viscosity.

The temperature-sensitive viscosification of low solids content solutions (1 wt % and 2 wt %) of a PAA-end modified poloxamer copolymer prepared as described in Example 1 is shown in FIG. 2. Rheological properties (storage modulus, G', loss modulus, G'', and loss angle δ°) are reported over a temperature range of 5–70° C. The storage modulus is a measure of the mechanical strength of the system, which increases upon increased solution viscosity. The loss modulus measures the liquidity of the system, which decreases upon viscosification. $\tan \delta^\circ$ is the relationship between the two, e.g., G''/G'. Even very dilute solutions exhibited a transition from Newtonian liquid at ambient temperature to a viscoelastic gel at body temperature.

Unlike many prior art hydrogels, e.g., carbomers, the poloxamer:poly(acrylic acid) composition does not permanently lose viscosity after being subjected to high shear conditions. The poloxamer:poly(acrylic acid) composition remains unaffected by such shear conditions as homogenization. No significant decrease in viscosity is observed.

A number of factors influence the viscosity and transition temperature of the composition. The more important factors include polymer concentration, pH and presence and nature of additives. Additives may be included which shift the temperature of viscosification upwards or downwards. Suitable additives are those which disrupt or enhance the micelle forming capabilities of the poloxamer, respectively.

The linear copolymer may be prepared using conventional polymer synthetic methodology. For example, a poloxamer may be chemically reacted at the terminal hydroxyl groups to provide a polymerizable moiety. The moiety may be further reacted with monomers or oligomers of acrylic acid to provide the end-modified copolymer. A general method of making the end-modified poloxamer compositions of the present invention comprises solubilization of an end-activated poloxamer component in a monomer of the bioadhesive polymer, e.g., acrylic acid monomer, followed by polymerization of the monomer. Polymerization may be accomplished by addition of a polymerization initiator or by irradiation techniques. The initiator may be a free radical initiator, such as chemical free radical initiators and UV or gamma radiation initiators. Conventional free radical initiators may be used according to the invention, including, but in no way limited to ammonium persulfate, benzoin ethyl ether, benzyl peroxide, 1,2'-azobis(2,4-dimethylpentanitrile) (Vazo 52) and azobisisobutyronitrile (AIBN). Initiation may also be accomplished using cationic or anionic initiators. Many variations of this methods will be apparent to one skilled in the art and are contemplated as within the scope of the invention. For example, the poloxamer component may be dissolved in an acrylic acid/water mixture instead of pure monomer. It may be desirable to remove unreacted monomer and/or free poloxamer from the resultant polymer network. This may be accomplished using conventional techniques, such as, by way of example, dialysis or Soxhlet extraction. The interested reader is directed to L. Bromberg, "Polyether-modified poly(acrylic acid) synthesis and properties," *Ind. Eng. Chem. Res.*, 37(11): 4267–4274 (1998), for further details.

The reverse viscosification effect at low polymer concentrations provides clear, colorless gels which are particularly well-suited to pharmaceutical and personal care applications. For example, very little residue is formed upon dehydration which may be important in some applications, such as in optically applied pharmaceuticals. An additional advantage of the composition of the invention is that it remains clear and translucent before and after the triggering environmental change. These characteristics of the reversibly gelling composition make it well suited for use in pharmaceutical compositions.

The practical advantage of this behavior of the composition is that the formulation can be administered as a flowing liquid at ambient temperatures. Upon contact with body tissues it viscosifies, thus changing its flow properties, and more importantly, its clearance from the site of application is dramatically reduced. Furthermore, for polymers in general, the viscosity at ambient temperature is concentration dependent. As the concentration is increased to achieve desired flow properties in contact with body tissues, the viscosity at ambient temperatures also increases, making it more difficult to administer such compositions.

Thus, a composition may be prepared at low temperatures while the composition is in a low viscosity state. Mixing of ingredients under low viscosity is expected to be easier, thus simplifying the manufacturing process. Yet, the resultant mixture would be of increased viscosity at use temperatures. As a further advantage, a composition comprising reversibly gelling composition may be spread thinly to allow for even application, due to its low viscosity at room temperature, but will thicken and "fill" the body contours upon warming up to body surface temperature.

The reversibly gelling composition may also be included in a composition for use as a stabilizing, solubilizing or emulsifying agent for a hydrophobic component of the formulation. Upon aggregation and/or micelle formation in the polyoxyalkylene component, hydrophobic domains are created which may be used to solubilize and control release of hydrophobic agents. Similar micelle-based systems have been shown to protect trapped peptides and proteins against enzymatic degradation from surface enzymes.

The reversible viscosification of the composition at elevated temperatures makes the materials ideal for use as thickening agents in pharmaceutical and personal care products at any temperature above the transition. Another use of the "thickening" of solutions containing the composition as a thickener supplement in emulsions. Currently emulsifiers are often negatively effected by increased temperatures. An additive with reverse thermal viscosification properties, however, would react in exactly the opposite way, increasing its ability to emulsify as it gained three-dimensional structure upon heating above its transition temperature.

In addition to the unique rheological properties provided by the reverse thermal composition, the reverse thermal composition is capable of solubilizing and releasing bioactive materials. Solubilization is expected to occur as a result of dissolution in the bulk aqueous phase or by incorporation of the solute in micelles created by the hydrophobic domains of the poloxamer. Release of the drug would occur through diffusion or network erosion mechanisms.

In the applications where the reversibly gelling polymer composition can act as a surfactant, the composition will have the ability to act as a primary emulsifier without any (or with very little) addition of traditional surfactant. The polyoxyalkylene composition will also act as a stabilizer for oil-soluble ingredients that would conventionally need to be

solubilized by oils in formulation. The hydrophobic portion of the composition (PPO) forms domains which act as reservoirs for an oil-soluble or hydrophobic additive, such as a hydrophobic pharmaceutical agent. The increase in viscosity above the transition temperature adds structure and yield value to the water phase and results in a highly stable emulsion for the hydrophobic additive.

The composition may be useful as a solubilization agent in pharmaceutical and personal care applications. A self-assembling system comprising the reversibly gelling composition exhibits thermogelation, pH sensitivity, and the ability to solubilize hydrophobic agents in aqueous media. When poloxamer is copolymerized with poly(acrylic acid) (PAA) according to the invention, the resulting composition is bioadhesive and can be applied in a number of therapies. The materials described in this invention combine "reverse" thermoviscosification mucoadhesion, solubilization of hydrophobic and difficult to manage moieties, easy formulation, and protection of agents from degradation to provide a superior medium for pharmaceutical and personal care products.

Those skilled in the art will appreciate that the composition compositions of the present invention may be utilized for a wide variety of pharmaceutical and personal care applications. To prepare a pharmaceutical composition, an effective amount of pharmaceutically active agent(s) which imparts the desirable pharmaceutical effect is incorporated into the reversibly gelling composition of the present invention. Preferably the selected agent is water soluble, which will readily lend itself to a homogeneous dispersion through out the reversibly gelling composition; however, the composition has been demonstrated to significantly solubilize or suspend hydrophilic agents in order to improve formulation homogeneity. It is also preferred that the agent(s) is nonreactive with the composition. For materials which are not water soluble, it is also within the scope of the invention to disperse or suspend lipophilic material throughout the composition.

A discussion of particular applications and formulations follows.

Esophageal, oral cavity and buccal applications. One indication for the use of this reverse thermal composition would be as a coating to protect tissue from external or internal chemical challenges. For example, the hydrogel in the form of an esophageal formulation could coat the esophagus and protect it from the effects of acid, resulting from gastric reflux (GERD). Because of its ionic nature, the neutralized, polyacrylic acid component of the reverse thermal composition could neutralize a certain amount of acid and prevent the acid from acting upon the tissue. In another variation, the reverse thermal composition formulation could include acid absorbing substances, such as, aluminum oxide.

With the incorporation of bioactive materials, the hydrogel provides a suitable vehicle for delivering drugs within the esophageal lining. As explained above, its rheological and mucoadhesive properties are desirable attributes for controlling and facilitating drug delivery. The shear sensitivity of the polymer could also be taken advantage of in applications in which a liquid treatment is sprayed under high shear conditions onto the oral cavity, where the solution adheres and viscosifies to provide a reservoir for antibacterial agents, such as chlorohexadine, or a breath freshener.

Ophthalmic applications. Most ophthalmic drugs are applied to the eye topically to the precorneal area. The most common dosage form is a liquid drop. Drug bioavailability

is generally low because liquid formulations are quickly cleared from the eye by tearing and blinking, resulting in the need for frequent dosing and uneven drug delivery.

The end-modified hydrogel composition provides a new vehicle for achieving greater bioavailability of topically administered ophthalmic drugs. Formulations containing it can be applied as drops which viscosify or gel upon contact with eye. Since gelling can be accomplished with low concentrations of the polymer, blurring can be minimized upon drop instillation. Low solid concentrations also help to minimize crusting along the eyelid margins.

A particular advantage of the hydrogel is that, as a result of its rheological properties, compositions containing the polymer will evenly coat the precorneal surface. This is in contrast to other ophthalmic drug delivery vehicles which may gel upon application to the eye but which form deposits of the formulation that reside under one eyelid. The ability of the polymer to shear-thinning or to evenly spread over the precorneal surface is particularly advantageous in dry eye formulations or in the treatment of inflammation and wound healing conditions.

The use of the end-modified hydrogel composition would be indicated for delivering bioactive materials, such as, anesthetics, mydriatics and cycloplegics, antimicrobial agents (antibacterial, antifungal, antiviral), anti-inflammatory agents, agents for the treatment of glaucoma, ocular decongestants, diagnostic agents, and wound healing agents.

Nasal applications. The use of the end-modified hydrogel composition is also indicated for the delivery of drugs to the nasal cavity. Nasal drug delivery has been considered as an alternative to parenteral routes of administration of drugs that demonstrate low oral bioavailability. In order to increase the bioavailability of nasally administered drugs, efforts have been made to increase the residence time of formulations in the nasal cavity. Nasal delivery of drugs can offer advantages over other methods of delivery, including rapid systemic absorption, lower dosing, more rapid onset of desired therapeutic effects, and improved pharmacokinetics. In addition, it provides an alternative route for administering peptide drugs, which generally have low bioavailability via the oral route and are normally administered parenterally.

The rheological properties of the reverse thermal composition are uniquely suited to nasal delivery systems. Earlier results demonstrated that formulation variables can be manipulated to significantly affect the higher temperature viscosity of the reverse thermal composition. These same variables have only minimal effects on the low temperature viscosity. Therefore, formulations containing the end-modified hydrogel composition can be readily sprayed at low temperature; the subsequent viscosification occurs only after administration of the formulation and only at the site of application.

The end-modified hydrogel composition is also useful for delivering agents such as decongestants, antihistamines, anti-osteoporosis agents, hormones, antineoplastic agents, Parkinsonism drugs, etc. The composition is also indicated for the application of vaccines, such as those against the influenza virus.

A further desirable outcome of the use of the end-modified hydrogel composition in the delivery of nasal formulations is the prevention of roll back, or the loss of the formulation by rapid flow to the posterior section of the nasal cavity and into the esophagus. In addition to the negative effects on the delivery of the drug across the desired mucosal tissue, roll can lead to unpleasant taste sensations associated with some drug formulations.

Another desirable outcome of the use of the end-modified hydrogel composition in the delivery of nasal formulations is the prevention of drip, or the loss of the formulation by flow outward due to gravity. In addition to the negative effects on the delivery of the drug across the desired mucosal tissue, drip leads to undesirable consumer appeal and therefore reduces the use of such drug formulations.

Vaginal/rectal applications. The use of the end-modified hydrogel composition is also indicated for the delivery of drugs to the vaginal or the rectal cavity. These drug delivery routes have been considered as an alternative to parenteral routes of administration of drugs that demonstrate low oral bioavailability. In order to increase the bioavailability of vaginally or rectally administered drugs, efforts have been made to increase the residence time of formulations in those cavities. These routes offer advantages over other methods of delivery, including rapid systemic absorption, lower dosing, more rapid onset of desired therapeutic effects, and improved pharmacokinetics.

The rheological properties of the reverse thermal composition are uniquely suited to both vaginal and rectal delivery systems. Such formulations containing the end-modified hydrogel composition can be readily applied at low temperature in a liquid or semi-liquid form to allow consumer preferred format for administration; the subsequent viscosification occurs only after administration of the formulation and only at the site of application to eliminate the leak-back that is typical undesired effect of current formulations.

Veterinary applications. The reversibly gelling composition of the invention also may be useful in the treatment of not only human conditions but in providing treatments for animal care. For veterinary products, the end-modified hydrogel composition is indicated for the preparation of topical dermal products, such as antibacterials, antifungals, antipruritics, and antiseborrhea, antiodor, and antiseptic/wound healing preparations. Otic products would include ear cleaners with or without actives, such as, antifungals. Ophthalmic products would include eye moisturizers or antimicrobial preparations. The rheological, solubilizing, drug delivery, and chemical properties provide the formulator of veterinary products the latitude to prepare compositions in a variety of delivery forms and, more importantly, with regard to companion animals, with a non-oily quality.

Tablet Excipients. It has been demonstrated that standard pharmaceutical processes, such as lyophilization and air-drying can process the hydrogel of the invention. The reversible thermal viscosifying hydrogel may be reconstituted with water, phosphate buffer or calcium chloride solution, without loss or degradation of the rheological properties of the polymer. Thus, it is contemplated that the hydrogel of the invention may also be incorporated as excipients into tablets or granules for oral delivery. The polymer may be coated on an outer surface of the tablet or may be introduced in powder form into the tablet along with the active agent and other ingredients. The poloxamer:poly (acrylic acid) composition may be used to promote bioadhesion of the tablet and its contents with the mucosal lining of the gastro-intestinal tract to extend transit time.

Also, when incorporated as a powder, the slow dissolution rate of the end-modified hydrogel makes it a suitable excipient to sustained release tableting formulation. The addition of such hydrogel would yield to a slow release of the incorporated drug.

Injectibles. The end-modified hydrogel composition of the invention is well-suited for use in injectable applications. A depot formulation may be prepared and administered at

low viscosity to a subdermal or intramuscular site, for example. The polymer will viscosify and form a depot site, which will slowly release the active agent. The reversible thermally viscosifying polymer network, upon contact with body fluids including blood or the like, undergoes gradual release of the dispersed drug for a sustained or extended period (as compared to the release from an isotonic saline solution). This can result in prolonged delivery (over, say 1 to 2,000 hours, preferably 2 to 800 hours) of effective amounts (say, 0.0001 mg/kg/hour to 10 mg/kg/hour) of the drug. This dosage form can be administered as is necessary depending on the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like.

Alternatively, the end-modified hydrogel composition may be prepared at higher viscosities in order to suspend microspheres or particles in the formulation. The formulation can then take advantage of the shear thinning properties of the polymeric material. Thus, during injection, the formulation is subjected to shear stresses which reduce viscosity and allow an ordinarily viscous formulation to be introduced into the patient by injection. Cessation of the strain results in reestablishing the high viscosity of the formulation, so that the active agent may be slowly released therefrom.

The end-modified hydrogel composition is effective in extending the duration of contact of preparations that have been applied to mucosal tissues. In providing a longer residence time, the reverse thermal composition provides a valuable tool for increasing drug delivery across mucosal surfaces.

The end-modified hydrogel composition also may be used for products in which there is no bioactive ingredient. The function of the composition would be to provide, for example, a protective or lubricating film to the surface of the tissue. For example, the composition could be the basic ingredient for a lubricating drop for the eye. By its nature, that is, that of a hydrogel, it could provide a long lasting lubricious and moisturizing film to the eye of individuals suffering from dry eye conditions due to pathological states or environmental stress. Other similar indications would be for nasal or vaginal moisturizers.

It will also be appreciated that a sterile environment may be required. It is contemplated as within the scope of the invention that the reversibly gelling composition compositions of the present invention may be prepared under sterile conditions.

In the preparation of pharmaceutical compositions, problems can be encountered in the solubilization of hydrophobic bioactive materials. Because of its hydrophobic moieties, the end-modified hydrogel composition is capable of facilitating such dissolution, even at the low concentrations which are used in formulating.

Preparation of pharmaceutical compositions may be accomplished with reference to any of the pharmaceutical formulation guidebooks and industry journals which are available in the pharmaceutical industry. These references supply standard formulations which may be modified by the addition or substitution of the reversible viscosifying composition of the present invention into the formulation. Suitable guidebooks include *Pharmaceuticals and Toiletries Magazine*, Vol. 111 (March, 1996); *Formulary: Ideas for Personal Care*; Croda, Inc, Parsippany, N.J. (1993); and *Pharmaceutical Formulary*, BASF, which are hereby incorporated in their entirety by reference.

The pharmaceutical composition may be in any form. Suitable forms will be dependant, in part, of the intended

mode and location of application. Ophthalmic and otic formulations are preferably administered in droplet or liquid form; nasal formulations are preferable administered in droplet or spray form, or may be administered as a powder (as a snuff); vaginal and rectal formulations are preferably administered in the form of a cream, jelly or thick liquid; veterinary formulations may be administered as a cream, lotion, spray or mousse (for application to fur or exterior surface); esophageal and buccal/oral cavity applications are preferably administered from solution or as a powder; film forming applications or dermal applications may be administered as a lotions, creams, sticks, roll-ons formulations or pad-applied formulations.

Exemplary drugs or therapeutics delivery systems which may be administered using the aqueous responsive composition compositions of the invention include, but are in no way limited to, mucosal therapies, such as esophageal, otic, rectal, buccal, oral, vaginal, and urological applications; topical therapies, such as wound care, skin care and teat dips; and intravenous/subcutaneous therapies, such as intramuscular, intrabone (e.g., joints), spinal and subcutaneous therapies, tissue supplementation, adhesion prevention and parenteral drug delivery. In addition, further applications include transdermal delivery and the formation of depots of drug following injection. It will be appreciated that the ionic nature of the biocompatible component of the responsive composition provides an adhesive interaction with mucosal tissue.

Because the reversibly gelling composition of the present invention is suited for application under a variety of physiological conditions, a wide variety of pharmaceutically active agents may be incorporated into and administered from the composition. The pharmaceutical agent that may be loaded into the polymer networks of the present invention are any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of suitable pharmaceutical agents that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present novel polymer networks.

The compositions of the invention include a safe and effective amount of a pharmaceutically active agent. "Safe and effective", as it is used herein, means an amount high enough to significantly positively modify the condition to be treated or the pharmaceutical effect to be obtained, but low enough to avoid serious side effects. As is mentioned herein above, compositions of the invention are considered to include both pharmaceutical agents which treat the source or symptom of a disease or physical disorder and personal care or cosmetic agents which promote bodily attractiveness or mask the physical manifestations of a disorder or disease.

Drugs that are not themselves liquid at body temperature can be incorporated into polymers, particularly gels. Moreover, peptides and proteins which may normally be lysed by tissue-activated enzymes such as peptidases, can be passively protected in gels as well. See, Gehrke et al. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, 22:145 (1995).

The variety of different therapeutic agents which can be used in conjunction with the copolymers of the invention is vast. In general, therapeutic agents which may be administered via the pharmaceutical compositions of the invention include, without limitation: anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations; anorexics; antihelmintics; antiarthritics; antiasthmatic agents; anticonvulsants; antidepressants; antidiuretic agents; antidiarrheals; antihistamines; antiinflammatory agents; antimigraine preparations; antinauseants; antineoplastics; antiparkinsonism drugs; antipruritics; antipsychotics; antipyretics, antispasmodics; anticholinergics; sympathomimetics; xanthine derivatives; cardiovascular preparations including calcium channel blockers and beta-blockers such as pindolol and antiarrhythmics; antihypertensives; diuretics; vasodilators including general coronary, peripheral and cerebral; central nervous system stimulants; cough and cold preparations, including decongestants; hormones such as estradiol and other steroids, including corticosteroids; hypnotics; immunosuppressives; muscle relaxants; parasympatholytics; psychostimulants; sedatives; and tranquilizers; and naturally derived or genetically engineered proteins, polysaccharides, glycoproteins, or lipoproteins. Suitable pharmaceuticals for parenteral administration are well known as is exemplified by the Handbook on Injectable Drugs, 6th edition, by Lawrence A. Trissel, American Society of Hospital Pharmacists, Bethesda, Md., 1990 (hereby incorporated by reference).

Pharmaceutical agents includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e. cyanobacteria).

The pharmaceutically active compound may be any substance having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide T, thyrocalcitonin, parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotrophic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules. The pharmaceutical agents may be selected from insulin, antigens selected from the group consisting of MMR (mumps, measles and rubella) vaccine, typhoid vaccine, hepatitis A vaccine, hepatitis B vaccine, herpes simplex virus, bacterial toxoids, cholera toxin B-subunit, influenza vaccine virus, bordetella pertussis virus, vaccinia virus, adenovirus, canary pox, polio vaccine virus, plasmodium

falciparum, bacillus calmette geurin (BCG), klebsiella pneumoniae, HIV envelop glycoproteins and cytokins and other agents selected from the group consisting of bovine somatotropine (sometimes referred to as BST), estrogens, androgens, insulin growth factors (sometimes referred to as IGF), interleukin I, interleukin II and cytokins. Three such cytokins are interferon- β , interferon- γ and tuftsin.

Examples of bacterial toxoids are tetanus, diphtheria, pseudomonas A, mycobacterium tuberculosis. Examples of HIV envelop glycoproteins are gp 120 and gp 160 for AIDS vaccines. Examples of anti-ulcer H_2 receptor antagonists are ranitidine, cimetidine and famotidine, and other anti-ulcer drugs are omeprazole, cefupride and misoprostol. An example of a hypoglycaemic agent is glizipide. Insulin is used for the control of diabetes.

Classes of pharmaceutically active compounds which can be loaded into the ind-modified hydrogel include, but are not limited to, anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) antiviral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants tranquilizers, anticonvulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, miotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics, prostaglandins, anti-depressants, antipsychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the *Pharmazeutische Wirkstoffe* (Von Kleemann et al. (Eds) Stuttgart/New York, 1987, incorporated herein by reference). A more complete list of suitable pharmaceutical agents can be found in WO 97/00275, which is hereby incorporated by reference.

Exemplary pharmaceutical agents considered to be particularly suitable for incorporation into the pharmaceutical composition of the invention with retention of therapeutic effectiveness and other advantageous properties include but are not limited to imidazoles, such as miconazole, econazole, terconazole, saperconazole, itraconazole, metronidazole, fluconazole, ketoconazole, and clotrimazole, luteinizing-hormone-releasing hormone (LHRH) and its analogues, nonoxynol-9, a GnRH agonist or antagonist, natural or synthetic progestin, such as selected progesterone, 17-hydroxyprogesterone derivatives such as medroxyprogesterone acetate, and 19-nortestosterone analogues such as norethindrone, natural or synthetic estrogens, conjugated estrogens, estradiol, estropipate, and ethinyl estradiol, bisphosphonates including etidronate, alendronate, tiludronate, resedronate, clodronate, and pamidronate, calcitonin, parathyroid hormones, carbonic anhydrase inhibitor such as felbamate and dorzolamide, a mast cell stabilizer such as xesterbergsterol-A, lodoxamine, and cromolyn, a prostaglandin inhibitor such as diclofenac and ketorolac, a steroid such as prednisolone, dexamethasone, fluormethylone, rimexolone, and lotepednol, an antihistamine such as antazoline, pheniramine, and histaminase, pilocarpine nitrate, a beta-blocker such as levobunolol and timolol maleate, a sunscreen agent, an acne medication such as salicylic acid, sulfur, resorcinol, resorcinol monoacetate, and benzoyl peroxide, an anti-dandruff medication such as coal tar, pyrrithione zinc, salicylic acid, selenium sulfide, and sulfur, a dermatological agent such as bath oils, emollients,

hydrating agents, astringents, antipruritics, protectants, keratin-softening agents, and hydrocortisone, hydroquinone, or nicotine.

As will be understood by those skilled in the art, two or more pharmaceutical agents may be combined for specific effects. The necessary amounts of active ingredient can be determined by simple experimentation.

This material meets many of the requirements for an optimum transmucosal delivery system for proteins, including peptides. Effective and efficient delivery involves four primary elements: a method of holding an optimal quantity of peptides against the mucosa for an extended period; a method of controlling the release of the peptides in a desired pattern (e.g., burst, sustained, circadian, etc.), transferring the peptides from the mucosal surface to the blood sera or other target, and maintenance of activity of peptides. The measure of merit is the reliable achievement of a desired pharmaceutical effect with minimal wasted active material—for example, the achievement and sustaining of an effective level of active peptide in the blood stream for a given time period with minimal excess delivery and minimal loss of activity through inactivation or erosion.

The composition of the invention can be chosen for protein delivery. The biocompatible polymer component can be a mucoadhesive material (acrylic acid). The component can be a material which erodes (acrylic acid) or one that degrades (hyaluronic acid). The backbone can be crosslinked, can involve co-monomers, and can be of varying molecular weights or structures. These modifications to the backbone directly effect retention of the Peptide-gel system, patterns of release, and peptide activity.

In addition to the poloxamer:poly(acrylic acid) hydrogel, additional pharmaceutically acceptable carriers may be included in the composition, such as by way of example only, emollients, surfactants, humectants, powders and other solvents.

Preservatives can be desirably incorporated into the pharmaceutical compositions of the invention to protect against the growth of potentially harmful microorganisms. Suitable preservatives include, but are not limited to, alkyl esters of para-hydroxybenzoic acid, hydantoin derivatives, parabens, propionate salts, triclosan, tricarbonyl, tea tree oil, alcohols, farnesol, farnesol acetate, hexachlorophene and quaternary ammonium salts, such as benzalkonium, and a variety of zinc and aluminum salts. Pharmaceutical chemists are familiar with appropriate preservatives and may select that which provides the required product stability. Preservatives are preferably employed in amounts ranging from about 0.0001% to 2% by weight of the composition.

Emollients can be desirably incorporated into the pharmaceutical compositions of the invention to provide lubricity to the formulation. Suitable emollients may be in the form of volatile and nonvolatile silicone oil, highly branched hydrocarbons and synthetic esters. Amounts of emollients may be in the range of about 0.1–30 wt %, and preferably about 1–20 wt %. A variety of oily emollients may be employed in the compositions of this invention. These emollients may be selected from one or more of the following classes: triglyceride esters; acetoglyceride esters; ethoxylated glycerides; alkyl esters of fatty acids having 10 to 20 carbon atoms; alkenyl esters of fatty acids having 10 to 20 carbon atoms; fatty acids having 10 to 20 carbon atoms; fatty alcohols having 10 to 20 carbon atoms; fatty alcohol ethers, such as ethoxylated fatty alcohols of 10 to 20 carbon atoms having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups; ether-esters

such as fatty acid esters of ethoxylated fatty alcohols; lanolin and derivatives; polyhydric alcohol esters; wax esters; bees-wax derivatives; vegetable waxes including carnauba and candelilla waxes; phospholipids; sterol including cholesterol and cholesterol fatty acid esters; and amides such as fatty acid amides, ethoxylated fatty acid amides, solid fatty acid alkanolamides.

Humectants may be added to the composition to increase the effectiveness of the emollient, to reduce scaling, to stimulate removal of built-up scale and improve skin feel. The amount of humectant may be in the range of about 0.5–30 wt % and preferably between 1–15 wt %.

By way of example only, in the case of antibiotics and antimicrobials may be included in the composition of the invention. Antimicrobial drugs preferred for inclusion in compositions of the present invention include salts of lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amantadine and the like.

Personal Care Applications: The reverse viscosification effect at low polymer concentrations provides clear, colorless gels that are particularly well suited for cosmetic applications. For example, very little residue is formed upon dehydration which may be important in some applications, such as in topically applied cosmetics. An additional advantage of the composition of the invention is that it remains clear and translucent above and below the critical temperature or pH. These characteristics of the reversibly gelling composition make it well suited for use in cosmetic compositions.

The composition of the present invention technology may be added to cosmetic formulations to increase the thickness and viscosity of the composition. The poloxamer:poly(acrylic acid) possesses hydrophobic regions capable of aggregation. Unlike conventional thickeners, the aggregation of the composition of the present invention is temperature sensitive. Thus, the inventive composition of the present invention may have a transition temperature (i.e. temperature of aggregation) above room temperature so that the cosmetic composition is of low viscosity at or below room temperature and is of high viscosity at or around body temperature (body temperature includes both surface and internal body temperature). Thus, a composition may be prepared at low temperatures while the composition is in a low viscosity state. Mixing of ingredients under low viscosity is expected to be easier, thus simplifying the manufacturing process. Yet, the resultant mixture would be of increased viscosity at use temperatures. As a further advantage, a cosmetic composition comprising poloxamer:poly(acrylic acid) may be spread thinly to allow for even application, due to its low viscosity at room temperature, but will thicken and “fill” the skin contours upon warming up to body surface temperature.

In another aspect of the invention, the composition may be applied through a nozzle that provides high shear to reduce viscosity, yet the composition regains its viscosity after application to the skin. This contrasts with conventional formulations which permanently lose viscosity after being subjected to high shear.

In another aspect of the invention, the composition may be formulated and applied as a liquid, spray, semi-solid gel,

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cream, ointment, lotion, stick, roll-on formulation, mousse, pad-applied formulation, and film-forming formulation.

The poloxamer:poly(acrylic acid) composition may also be included in a personal care or cosmetic composition for use as a stabilizing, solubilizing or emulsifying agent for a hydrophobic component of the cosmetic formulation. The strong hydrophilic regions of the poloxamer resulting from aggregation and micelle formation create hydrophobic domains which may be used to solubilize and control release of hydrophobic agents. Similar micelle-based systems have been shown to protect trapped peptides against enzymatic degradation from surface enzymes.

Those skilled in the art will appreciate that the composition compositions of the present invention may be utilized for a wide variety of cosmetic and personal care applications. To prepare a cosmetic composition, an effective amount of cosmetically active agent(s) that imparts the desirable cosmetic effect is incorporated into the reversibly gelling composition of the present invention. Preferably the selected agent is water soluble, which will readily lend itself to a homogeneous dispersion through out the reversibly gelling composition; however, the composition has been demonstrated to significantly solubilize or suspend hydrophilic agents in order to improve formulation homogeneity. It is also preferred that the agent(s) is nonreactive with the composition. For materials which are not water soluble, it is also within the scope of the invention to disperse or suspend powders or oil (lipophilic materials) throughout the composition. It will also be appreciated that some applications may require a sterile environment. It is contemplated as within the scope of the invention that the reversibly gelling composition compositions of the present invention may be prepared under sterile conditions. An additional feature of the reversibly gelling polymer composition is that is prepared from constituent polymers that have known accepted toxicological profiles.

Exemplary cosmetic and personal care applications, for which the reversibly gelling composition may be used include, but are not limited to, baby products, such as baby shampoos, lotions, powders and creams; bath preparations, such as bath oils, tablet and salts, bubble baths, bath fragrances and bath capsules; eye makeup preparations, such as eyebrow pencil, eyeliner, eye shadow, eye lotion, eye makeup remover and mascara; fragrance preparations, such as colognes and toilet waters, powders and sachets; noncoloring hair preparations, such as hair conditioner, hair spray, hair straighteners, permanent waves, rinses shampoos, tonics, dressings and other grooming aids; color cosmetics; hair coloring preparations such as hair dye, hair tints, hair shampoos, hair color sprays, hair lighteners and hair bleaches; makeup preparations such as face powders, foundations, leg and body paints, lipstick, makeup bases, rouges and makeup fixatives; manicuring preparations such as basecoats and undercoats, cuticle softeners, nail creams and lotions, nail extenders, nail polish and enamel, and nail polish and enamel remover; oral hygiene products such as dentrifices and mouthwashes; personal cleanliness, such as bath soaps and detergents, deodorants, douches and feminine hygiene product; shaving preparations such as after-shave lotion, beard softeners, men's talcum, shaving cream, shaving soap and preshave lotions; skin care preparations such as cleansing preparations, skin antiseptics, depilatories, face and neck cleansers, body and hand cleansers, foot powders and sprays, moisturizers, night preparations, paste masks, and skin fresheners; and suntan preparations such as suntan creams, gels and lotions, indoor tanning preparations.

Preparation of the above-named cosmetic compositions and others may be accomplished with reference to any of the

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cosmetic formulation guidebooks and industry journals which are available in the cosmetic industry. These references supply standard formulations which may be modified by the addition or substitution of the reversible viscosifying composition of the present invention into the formulation. Suitable guidebooks include *Cosmetics and Toiletries Magazine*, Vol. 111 (March, 1996); *Formulary: Ideas for Personal Care*; Croda, Inc, Parsippany, N.J. (1993); and *Cosmeticon: Cosmetic Formulary*, BASF, which are hereby incorporated in their entirety by reference.

The cosmetic composition may be in any form. Suitable forms include but are not limited to lotions, creams, sticks, roll-ons formulations, mousses, aerosol sprays, pad-applied formulations, and film-forming formulations.

As those skilled in the art will appreciate, the foregoing list is exemplary only. Because the reversibly gelling composition of the present invention is suited for application under a variety of physiological conditions, a wide variety of cosmetically active agents may be incorporated into and administered from the composition. In addition to the poloxamer:poly(acrylic acid) polymer network, additional cosmetically acceptable carriers may be included in the composition, such as by way of example only, emollients, surfactants, humectants, powders and other solvents. By way of example only, the cosmetic composition also may include additional components, which serve to provide additional aspects of the cosmetic affect or to improve the stability and/or administration of the cosmetic. Such additional components include, but are not limited to, preservatives, abrasives, acidulents, antiacne agents, antiaging agents, antibacterials, anticaking, anticaries agents, anticellulites, antidandruff, antifungal, anti-inflammatories, anti-irritants, antimicrobials, antioxidants, astringents, anitperspirants, antiseptics, antistatic agents, astringents, binders, buffers, additional carriers, chelators, cell stimulants, cleansing agents, conditioners, deodorants, dipilatories, detergents, dispersants, emollients, emulsifiers, enzymes, essential oils, exfoliants, fibers, film forming agents, fixatives, foaming agents, foam stabilizers, foam boosters, fungicides, gellants, glosser, hair conditioner, hair set resins, hair sheen agents, hair waving agents, humectants, lubricants, moisture barrier agents, moisturizers, ointment bases, opacifier, plasticizer, polish, polymers, powders, propellant, protein, refatting agents, sequestrant, silicones, skin calming agents, skin cleansers, skin conditioners, skin healing, skin lightening agents, skin protestants, skin smoothing agents, skin softening agents, skin soothing agents, stabilizers, sunscreen agents, surfactants, suspending agents, tanning accelerators, thickeners, vitamins, waxes, wetting agents, liquefiers, colors, flavors and/or fragrances. Suitable materials which serve the additive functions listed here are well known in the cosmetic industry. A listing of the additive function and materials suitable for incorporation into the cosmetic composition may be found in Appendix A, which is appended hereto at the end of the specification. Further information may be obtained by reference to *The Cosmetic Bench Handbook*, Cosmetics & Toiletries; C. C. Urbano, editor, Allured Publ. Corp., 1996, which is hereby incorporated in its entirety by reference.

A brief description of some preferred additives and cosmetically active agents follows. The compositions of the invention include a safe and effective amount of a cosmetically active agent. "Safe and effective", as it is used herein, means an amount high enough to significantly positively modify the condition to be treated or the cosmetic effect to be obtained, but low enough to avoid serious side effects.

Preservatives and emollients can be desirably incorporated into the cosmetic compositions of the invention, such as those described above for pharmaceutical compositions. A variety of oily emollients may be employed in the compositions of this invention. These emollients may be selected from one or more of the following classes: 1. Triglyceride esters such as vegetable and animal fats and oils. Examples include castor oil, cocoa butter, safflower oil, cottonseed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, squalene, Kikui oil and soybean oil; 2. Acetoglyceride esters, such as acetylated monoglycerides; 3. Ethoxylated glycerides, such as ethoxylated glyceryl monostearate; 4. Alkyl esters of fatty acids having 10 to 20 carbon atoms, such as, methyl, isopropyl, and butyl esters of fatty acids, and including hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, decyl oleate, isodecyl oleate, hexadecyl stearate decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldodecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate; 5. alkenyl esters of fatty acids having 10 to 20 carbon atoms, such as oleyl myristate, oleyl stearate, and oleyl oleate and the like; 6. fatty acids having 10 to 20 carbon atoms, such as pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic, and erucic acids and the like; 7. fatty alcohols having 10 to 20 carbon atoms, such as, lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecanyl alcohols are examples of satisfactory fatty alcohols and the like, 8. fatty alcohol ethers, such as ethoxylated fatty alcohols of 10 to 20 carbon atoms including the lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols, having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups; 9. ether-esters such as fatty acid esters of ethoxylated fatty alcohols; 10. Lanolin and derivatives, such as lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases and the like; 11. polyhydric alcohol esters, such as, ethyleneoxide mono and di-fatty acid esters, diethyleneoxide mono-and di-fatty acid esters, polyethyleneoxide (200-6000) mono- and di-fatty acid esters, propyleneoxide mono- and di-fatty acid esters, polypropyleneoxide 2000 monooleate, polypropyleneoxide 2000 monostearate, ethoxylated propyleneoxide monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol polyfatty esters, ethoxylated glyceryl monostearate, 1,2-butylene glycol monostearate, 1,2-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters; 12. wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate; 13. beeswax derivatives, e.g. polyoxyethylene sorbitol beeswax; 14. vegetable waxes including carnauba and candelilla waxes; 15. phospholipids such as lecithin and derivatives; 16. sterol including cholesterol and cholesterol fatty acid esters; 17. amides such as fatty acid amides, ethoxylated fatty acid amides, solid fatty acid alkanolamides.

Humectants may be added to the composition to increase the effectiveness of the emollient, to reduce scaling, to stimulate removal of built-up scale and improve skin feel.

By way of example only, suitable humectants include polyhydric alcohols, such as glycerol, polyalkylene glycols, alkylene polyols their derivatives, propyleneoxide, dipropyleneoxide, polypropyleneoxide, polyethyleneoxide, sorbitol, hydroxypropyl sorbitol, hexylene glycol, 1,3-butylene glycol, 1,2,6-hexanetriol, ethoxylated glycerol, propoxylated glycerol and the like. The amount of humectant may be in the range of about 0.5-30 wt % and preferably between 1-15 wt %.

In topical skin care applications, a variety of active substances may be advantageously employed. By way of example only suitable active agents which may be incorporated into the cosmetic composition include anti-aging active substances, anti-wrinkle active substances, hydrating or moisturizing or slimming active substances, depigmenting active substances, substances active against free radicals, anti-irritation active substances, sun protective active substances, anti-acne active substances, firming-up active substances, exfoliating active substances, emollient active substances, and active substances for the treating of skin disorders such as dermatitis and the like.

By way of example only, in the case of hydration, one or more moisturizers may be used, such as glycerin or urea, in combination with one or more precursor agents for the biosynthesis of structural proteins, such as hydroxyproline, collagen peptides and the like.

By the way of example only, in case of slimming, at least one ketolytic agent or an alpha-hydroxyacid such as salicylic acid or 5-n-octanoic acid may be used in combination with at least one liporegulating agent such as caffeine.

By way of example only, in the case of depigmentation, at least one keratolytic agent is used in combination with a depigmenting agent such as hydroquinone, tyrosinase inhibitor (koscic acid), ascorbic acid, kojic acid and sodium metabisulfite and the like.

By way of example only, in the case of protection against free radical agents, vitamin E (against COO. radicals), superoxide dismutase (against O₂.free radicals) and sugar and caffeine (against OH.free radicals).

By way of example only, in the case of anti-aging, moisturizers, sunscreens, alpha-hydroxyacids, salicylic acid or surface restructuring agents may be used in combination with enzymes for the repair of DNA, vascular protective agents or phospholipids rich in oligoelements and polyunsaturated fatty acids.

By way of example only, in the case of anti-acne agents, keratolytics, such as salicylic acid, sulfur, lactic acid, glycolic, pyruvic acid, urea, resorcinol and N-acetylcysteine, and retinoids, such as retinoic acid and its derivatives may be used.

By way of example only, in the case of anti-inflammation, non-steroidal anti-inflammatory agents (NSAIDS) may be used, such as propionic acid derivatives, acetic acid, fenamic acid derivatives, biphenylcarboxylic acid derivatives, oxicams, including but not limited to aspirin, acetaminophen, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenbufen, ketoprofen, indoprofen, pirofen, carprofen, and bucloxic acid and the like.

By way of example only, in the case of antibiotics and antimicrobials may be included in the composition of the invention. Antimicrobial drugs preferred for inclusion in compositions of the present invention include salts of -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amantadine and the like.

By way of example only, in the case of sunscreen protection, suitable agents include 2-ethylhexyl p-methoxycinnamate, 2-ethylhexyl N,N-dimethyl-p-aminobenzoate, p-aminobenzoic acid, 2-phenyl p-methoxycinnamate, 2-ethylhexyl octocrylene, oxybenzone, homomenthyl salicylate, octyl salicylate, 4,4'-methoxy-1-butylidibenzoylmethane, 4-isopropyl dibenzoylmethane, 3-benzylidene camphor, 3-(4-methylbenzylidene) camphor, titanium dioxide, zinc oxide, silica, iron oxide, and mixtures thereof and the like. The sunscreens disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range. These sunscreens provide higher efficacy, broader UV absorption, lower skin penetration and longer lasting efficacy relative to conventional sunscreens. Generally, the sunscreens can comprise from about 0.5% to about 20% of the compositions useful herein. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF). SPF is a commonly used measure of photoprotection of a sunscreen against erythema.

By way of example only, in the case of sunless tanning agents include, dihydroxyacetone, glyceraldehyde, indoles and their derivatives, and the like.

The composition may include cleansing surfactants. Cleansing surfactants are cationic, anionic, amphoteric or non-ionic surfactants which are water-soluble and produce a consumer-acceptable amount of foam. Nonionic surfactants are well-known materials and have been used in cleansing compositions. Therefore, suitable nonionic surfactants include, but are not limited to, compounds in the classes known as alkanolamides, block copolymers of ethylene and propylene, ethoxylated alcohols, ethoxylated alkylphenols, alkyl polyglycosides and mixtures thereof. In particular, the nonionic surfactant can be an ethoxylated alkylphenol, i.e., a condensation product of an alkylphenol having an alkyl group containing from about 6 to about 12 carbon atoms in either a straight chain or branched chain configuration with ethylene oxide, the ethylene oxide being present in an amount equal to at least about 8 moles ethylene oxide per mole of alkylphenol. Examples of compounds of this type include nonylphenol condensed with about 9.5 moles of ethylene oxide per mole of phenol; dodecylphenol condensed with about 12 moles of ethylene oxide per mole of phenol; dinonylphenol condensed with about 15 moles of ethylene oxide per mole of phenol; octylphenol condensed with about ten moles of ethylene oxide per mole of phenol; and diisooctyl phenol condensed with about 15 moles of ethylene oxide per mole of phenol.

A wide variety of acids, bases, buffers, and sequestrants can be utilized to adjust and/or maintain the pH and ionic strength of the compositions useful in the instant invention. Materials useful for adjusting and/or maintaining the pH and/or the ionic strength include sodium carbonate, sodium hydroxide, hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, sodium citrate, sodium bicarbonate, triethanolamine, EDTA, disodium EDTA, tetrasodium EDTA, and the like.

The composition may be useful as a solubilization agent in cosmetic and personal care applications. A self-assembling system comprising the reversibly gelling composition exhibits thermogelation, pH sensitivity, and the ability to solubilize hydrophobic agents in aqueous media. When poloxamer is copolymerized with poly(acrylic acid) (PAA) according to the invention, the resulting composition is bioadhesive and can be applied in a number of therapies.

The materials described in this invention combine "reverse" thermoviscosification mucoadhesion, solubilization of hydrophobic and difficult to manage moieties, easy formulation, and protection of agents from degradation to provide a superior medium for cosmetic and personal care products.

The reversible viscosification of the composition at elevated temperatures makes the materials ideal for use as thickening agents in cosmetic and personal care products at any temperature above the transition. Another use of the "thickening" of solutions containing the composition as a thickener supplement in emulsions. Currently emulsifiers are often negatively effected by increased temperatures. An additive with reverse thermal viscosification properties, however, would react in exactly the opposite way, increasing its ability to emulsify as it gained three-dimensional structure upon heating above its transition temperature.

In the applications where the reversibly gelling polymer composition can act as a surfactant, the composition will have the ability to act as a primary emulsifier without any (or with very little) addition of traditional surfactant. The responsive composition will also act as a stabilizer for oil-soluble ingredients that would conventionally need to be solubilized by oils in formulation. The hydrophobic portion of the composition (PPO) forms domains which act as reservoirs for an oil-soluble or hydrophobic additive, such as an oil droplet, as is illustrated in FIG. 1. These two features of the material of the invention would enable it to be used as a base in a cosmetic formulation that would be non-greasy due to lack of oils, such as petrolatum and mineral oil. The increase in viscosity above the transition temperature adds structure and yield value to the water phase and results in a highly stable emulsion.

Thus, poloxamer:poly(acrylic acid) composition compositions are valuable materials in the formulation of cosmetic and personal care products. In particular, they may be useful as rheology modifiers, provide a cushioning effect on the skin, offer barrier properties and controlled release of actives. In addition, the polymer composition may serve as a surfactant and is compatible with most ingredients used in the cosmetic industry. The above properties of the poloxamer:poly(acrylic acid) composition provides a cosmetic composition that spreads evenly and smoothly and which leaves a lubricious feel to the skin.

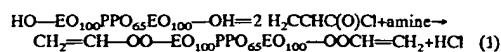
A wide variety of acids, bases, buffers, and sequestrants can be utilized to adjust and/or maintain the pH and ionic strength of the compositions useful in the instant invention. Materials useful for adjusting and/or maintaining the pH and/or the ionic strength include sodium carbonate, sodium hydroxide, hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, sodium citrate, sodium bicarbonate, triethanolamine, EDTA, disodium EDTA, tetrasodium EDTA, and the like.

The invention is described with reference to the following examples which are presented for the purpose of illustration only and are not limiting of the invention.

EXAMPLE 1

The example describes the synthesis of poloxamer:poly(acrylic acid) block copolymer.

A poloxamer was derivatized to obtain an acryloyl-terminated poloxamer according to the following equation.

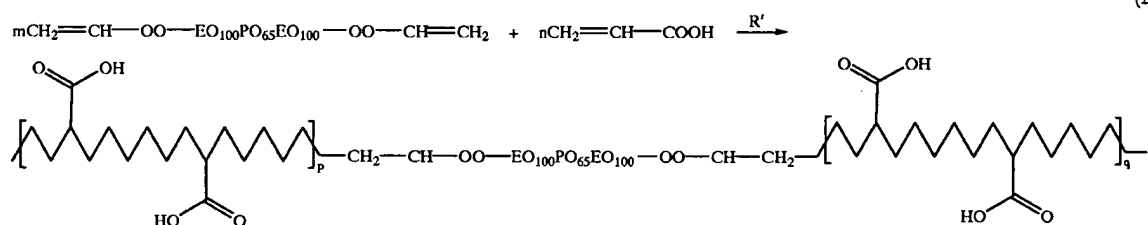


Pluronic F127 (EO₁₀₀PPO₆₅EO₁₀₀; 30 g; BASF, Germany) was dissolved in dry toluene in a 250 mL round bottomed

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flask equipped with a magnetic stirrer and gas inlet-outlet to which 2.1 g triethylamine (Aldrich, 99+%) was added dropwise while stirring at 50° C. under nitrogen blanket. Then 1.2 mL of acryloyl chloride (Aldrich, 96%) was added dropwise into the flask. followed by addition of 0.75 mL triethylamine in 5 mL toluene under constant flow of nitrogen. The reaction mixture was stirred at 50° C. for 1.5 h and the contents were cooled to ambient temperature and filtered. All liquids were evaporated under vacuum and the resulting polymer flakes were redissolved in 200 mL toluene and precipitated by addition of hexane. The steps of dissolution and precipitation were repeated, and the polymer was finally dissolved in a minimum amount of methylene chloride and washed with excess hexane in a separation funnel. The polymer was then dried under vacuum (10⁻³ Torr) at 20° C.

The acryloyl-modified poloxamer was then end-linked with poly(acrylic acid) by free radical polymerization according to eq (2).



Acrylic acid (30 g Aldrich, 99%) was neutralized by addition of 50 wt % aqueous NaOH solution while stirring. The degree of neutralization of acrylic acid was 6 mol %. Upon redissolution of precipitate, acryloyl-terminated poloxamer was charged into a flask and allowed to completely dissolve in acrylic acid under constant agitation. A 500 mL multi-necked thermostated flanged glass reactor equipped with a mechanical stirrer, syringe sampler, thermometer, programmable heater bath, and a gas inlet/outlet was charged with 400 mL of poly(vinyl alcohol) (99% hydrolyzed, MW 13,000, Aldrich) solution in dodecane and was deoxygenated overnight by nitrogen flow while stirring. A freshly prepared initiator system comprising 5 mL of freshly prepared ammonium persulfate (Aldrich, 99.9+%; 300 mg) and N,N,N',N'-tetramethylethylenediamine (Aldrich, 99.5%; 0.1 mL) in water/acrylic acid mixture was added into the solution of poloxamer in acrylic acid while stirring. The resulting solution was immediately introduced into the reactor under nitrogen blanket while stirring. The reactor was allowed to equilibrate at ambient temperature, the nitrogen flow was discontinued and the slurry of the resulting polymer was filtered off using Whatman filter paper (retention 10 μm). The polymer was repeatedly washed with excess heptane and then with excess hexane in a separation funnel. The resultant white powder was dried under vacuum at 40° C. for 24 h.

The material was evaluated for thermal-responsiveness. The results are reported in FIG. 2.

EXAMPLE 2

The example describes the synthesis of poloxamer:poly(acrylic acid) block copolymer. The acryloyl-terminated poloxamer of Example 1 was end-linked with poly(acrylic acid) as follows.

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Acrylic acid (40 g) was partially neutralized by addition of 50 w/w % aqueous NaOH solution while stirring. The degree of neutralization of acrylic acid was 6 mol %. Upon redissolution of precipitate, acryloyl-terminated poloxamer was charged into a flask and allowed to completely dissolve in acrylic acid under constant agitation. A 500 mL multi-necked, thermostated flanged glass reactor equipped with a mechanical stirrer, syringe sampler, thermometer, programmable heater bath, and a gas inlet/outlet was charged with 400 mL of 0.4% solution of poly(vinylpyrrolidinone-co-1-hexadecane) (International Specialty Products) in dodecane (Aldrich, 99%) and was deoxygenated overnight by nitrogen flow while stirring. A freshly prepared initiator system comprising a solution of lauryl peroxide (140 mg) and 2,2'-bisazo(2,4-dimethylpentanenitrile) (50 mg) in a small amount of acrylic acid was added into the solution of poloxamer in acrylic acid while stirring. The resulting solution was deoxygenated by nitrogen flow for 1 h and introduced into the reactor under

(2)

nitrogen blanket while stirring. The reactor was equilibrated for 1 h while stirring at 20° C. under nitrogen purge introduced from the bottom of the reactor. Then at t=0, heating began and timing commenced.

The reactor was heated up to 70° C. at a rate of 1.5° C./min under constant nitrogen flow. At a certain temperature, exothermic reaction caused a rapid temperature increase inside the reactor. Then heat increase subsided and the reactor cooled to 70° C. and was maintained at this temperature for 8–10 h under stirring. The reactor was allowed to equilibrate at 20° C., the nitrogen flow was discontinued and the slurry of the resulting polymer was repeatedly washed with heptane and then with excess hexane in separation funnels. The resultant white powder was dried under vacuum at 40° C. for 24 h.

Size-exclusion chromatography (SEC) of the poloxamer-poly(acrylic acid) copolymers was run at various temperatures on a Shimadzu LC-10A Series high pressure liquid chromatograph (HPLC) set up with a Viscotek SEC³ Tripole Detector System which included a laser scattering detector (scattering angle 90°; wavelength 670 nm; output power 126 mW; cell volume 12 μL), differential Wheatstone bridge viscometer (sensitivity 1×10⁻⁵ η_{sp}; shear rate 3000 s⁻¹; cell volume 50 μL), and a differential laser refractometer (wavelength 670 nm; sensitivity 3×10⁻⁸ Δn; shear rate 3000 s⁻¹; cell volume 8 μL). A 0.10–1.0 mg/mL sample of polymer solution was loaded onto a PL aquagel-OH mixed, 40, and 60 analytical temperature-controlled 3-column system (particle size 8 or 15 μm; dimensions 3×7.5 mm, Polymer Laboratories, Inc.) And then eluted using selected buffer. The SEC system was calibrated in the molecular weight (MW) range of 10³–10⁷ using poly(sodium acrylate) standards (American Polymer Standards Co.). For buffer preparation, ultrapure water from a Millipore Q purification

system (conductivity less than 0.05 μ S, outlet water filtered through a 0.22 μ m filter) was used. Prior to use, polymer samples were dialyzed against excess buffer at 4° C. for 24 h with a Spectra/Por® cellulose ester membrane (molecular weight cut-off 500). For fractionation, PL aquagel-OH 40 and 60 preparative columns (particle size 10 μ m; dimensions 300x25 mm) were used. Buffers contained 50 or 100 mM Na₂HPO₄ and varying concentrations of NaNO₃. pH was adjusted to 7.0 by addition of 1.0 M H₃PO₄, as needed. To achieve optimum reliability of the SEC measurements, the effect of the Donnan salt exclusion was studied by varying NaNO₃ concentrations. The area of the salt peaks was minimized when ionic strength of the buffer was 0.3 and 0.1 M for PAA and poloxamer-PAA samples, respectively. This observation agreed well with reported optimum salt concentrations for PAA standards. See, Kato et al., *Polymer* 25:218 (1984). Number-weight value for poloxamer-PAA was found to be 2.3×10^6 ; z-average molar masses for poloxamer-PAA was found to be 2.9×10^6 ; and a values for poloxamer-PAA was found to be 3.3×10^6 . Here, constants α and K are parameters of the Mark-Houwink equation ($[\eta] = K M^\alpha$). See, Cooper A. R., in *Polymers: Polymer Characterization and Analysis*, J. I. Kroschwitz, Ed., Wiley, New York, 1990, p. 481.

The resulting copolymer was characterized by NMR and IR as follows.

¹H-NMR (D₂O, 20° C., 10%): δ 3.7 (m, methylene HC—OC), 3.51 (m, methylene, HC—OC), 2.55, 2.15 (m, methine, HC—COONa), 1.55 (m, methylene, HC—COONa), 1.16 (s, CH₃ in PPO).

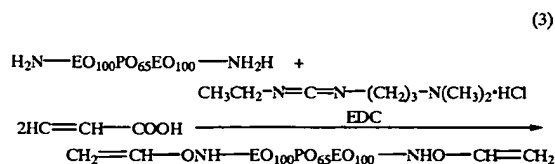
IR (KBR): 1740 (COONa and COOH), 1100 cm⁻¹ (COC).

Aggregation of the poloxamer-PAA polymer in 1% aqueous solution (pH 7.0) is illustrated in FIG. 3, in which FIG. 3A displays the change of storage modulus G' with temperature and FIG. 3B shows the change of loss modulus G'' with temperature. The storage modulus of the solution increases with temperature indicating transition from Newtonian-like liquid to a gel with significant elastic modulus.

An electronic spectrum of the 1% poloxamer-PAA sample (measured using a Shimadzu 1601PC UV-vis spectrophotometer equipped with a thermostated quartz cell with a 1 cm path length) is shown in FIG. 4. The solution shows electronic absorbance at 37° C. below 0.04 in the visible range and this is completely translucent to the human eye.

EXAMPLE 3

This example illustrates the method of synthesis of N-acryloyl-terminated poloxamer according to the following equation (3) and the formation of a poloxamer-PAA copolymer therefrom.



Amino-terminated poloxamer was synthesized as described by Chen et al. In "Temperature-Induced Gelation Pluronic-g-poly(acrylic acid) Graft Copolymers for Prolonged Drug Delivery to the Eye" in *Poly(ethylene glycol)*

Chemistry and Biological Applications, (J. M. Harris and S. Zalipski, Eds. ASC Symp. Ser 680, 12997 pp441-457), except that Pluronic F127 NF was used and both ends of the Pluronic oligomer were functionalized. Then conjugation of acrylic acid and amino-terminated Pluronic F127 NF was accomplished by simultaneous activation and coupling with a water-soluble condensing agent, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), as shown in eq. (3). The amino-terminated poloxamer and EDC components were dissolved at concentrations of 10 mg/mL, and 2 mg/mL in 10 mM phosphate buffer (pH 7.4) at 4° C. The mixture was then gently shaken for 24 h at 4° C. The reaction mixture was then dialyzed against excess deionized water at 4° C. for 48 h using Spectra/Por® cellulose ester membrane (MW cut-off 55, Spectrum®, Laguna Hills, Calif.) and passed through a PL-SCX semi-preparative cation-exchange column (1000 Å, 8 μ m, 100x10 mm, Polymer Laboratories, Inc. Amherst, Mass.) at a flow rate of 0.5 mL/min with 10 mM phosphate buffer as an eluent. The fraction absorbance was monitored at 215 nm. The resulting polymer was dried under high vacuum (10^{-5} Torr) at 30° C.

The resulting polymer had a characteristic vinyl stretch at 1640 cm⁻¹ in FTIR spectrum and UV maximum at λ 215 nm was observed in the electronic spectrum. As a control, a mixture of amino-activated Pluronic F127 NF and acrylic acid mer was run without addition of the EDC activation reagent. After the same treatment as above, no UV maximum at λ 215 nm was observed.

The thus obtained acryloyl-terminated poloxamer was end-linked with poly(acrylic acid) as follows. Acryloyl-terminated poloxamer (3 g) was dissolved in acrylic acid (99%, Aldrich; 5 g) and the solution was charged into a 100-mL multinecked, thermostated flanged glass reactor equipped with a mechanical stirrer, syringe sampler, thermometer, programmable heater bath, and a gas inlet/outlet. The reactor was charged with 30 mL of 1% poly(vinyl alcohol) (99% hydrolyzed, MW 13,000, Aldrich) solution in dodecane and was deoxygenated for 2 h by nitrogen flow while stirring. A freshly prepared initiator system comprising 1 mL of freshly prepared ammonium persulfate (Aldrich, 99.9+%; 10 mg) and N,N,N',N'-tetramethylethylenediamine (Aldrich, 99.5%; 0.02 mL) in water/acrylic acid mixture was added into the solution of poloxamer in acrylic acid while stirring. The solution was equilibrated for 24 h at 4° C. under nitrogen purge introduced from the bottom of the reactor. The reactor was allowed to equilibrate at ambient temperature, the nitrogen flow was discontinued and the slurry of the resulting polymer was filtered off using Whatman filter paper (retention 10 μ m). The polymer was repeatedly washed with excess heptane and then with excess hexane in a separation funnel. The resultant white powder was dried under vacuum at 40° C. for 24 h.

The resulting copolymer was characterized by NMR and IR as follows.

¹³C-NMR (D₂O, 20° C., 10%): δ 183 (ester COOH) 156 (urethane) 76-70 (ether COC) 46-37 (primary C—O and secondary C—C), 17.9 (CH₃ of PPO).

IR (KBR): 2939 (methyl CH of PPO), 1685 (C=O), 1220 (ester C—O stretch), 1099 (antisym and sym COC stretch) cm⁻¹.

The material was evaluated for thermal-responsiveness. The results are reported in FIG. 5. Viscosity in equilibrium flow experiments of a 2% aqueous solution (pH 7.0) indicates that the solution viscosity at body temperature. The viscous gels were sheared by the applied stresses.

EXAMPLE 5

The synthesis of poly(oxyethylene-co-oxypropylene-co-oxyethylene) diacrylate is described.

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The following steps are carried out using the procedures described previously in Example 1. Pluronic F127 NF (30.0 g) is dissolved in dry toluene (250 mL) and heated to 50° C. in a round-bottom flask equipped with magnetic stirrer and a gas inlet-outlet. Triethylamine (2.1 g) is added dropwise while stirring at 50° C. under nitrogen blanket. Acryloyl chloride (1.2 mL) is added dropwise into the reaction flask. In a separate container triethylamine (0.75 mL) is dissolved in toluene (5 mL.) and added dropwise to the reaction flask under constant flow of nitrogen. The reaction mixture is stirred at 50° C. for 1.5 h. The reaction vessel is cooled to ambient temperature (25° C.). When it reaches ambient temperature the solution is filtered. The solids are discarded. This solution is added slowly to hexane (1,250 mL) and the polymer is precipitated. The procedure of redissolution and precipitation was repeated. The resulting polymer is repeatedly dissolved in minimum amount of methylene chloride and washed with excess hexane in separation funnel. The polymer is then dried under vacuum at 20° C.

EXAMPLE 6

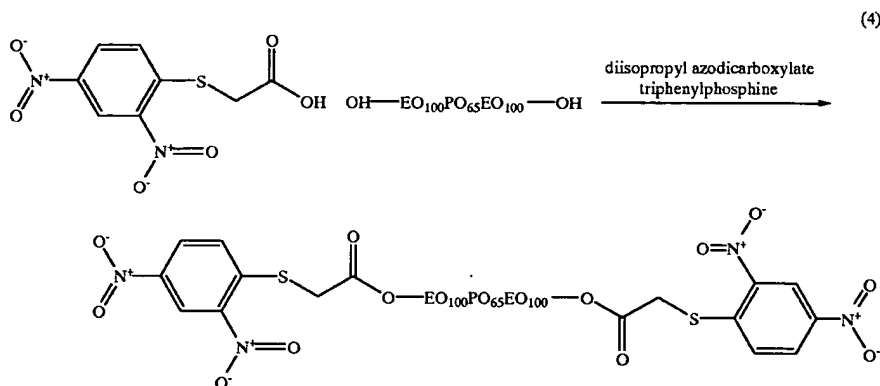
This example describes the synthesis of copolymers of modified Pluronic F127 poloxamer and poly(acrylic acid).

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The poloxamer is end-activated with sulfhydryl functionality which serves as a chain-transfer agent for polymerization of acrylic acid, followed by conjugation of the poloxamer and polymerized acrylic acid.

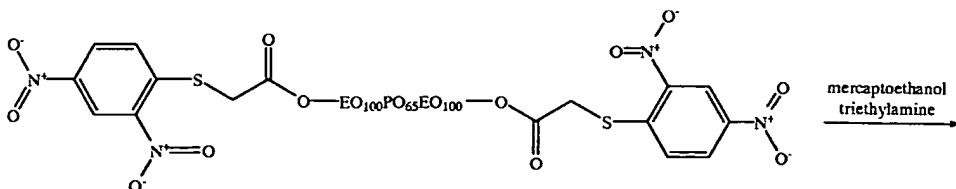
2,4-dinitrophenylacetic acid was synthesized as follows. Mercaptoacetic acid (97%, Aldrich, 5 g, 54 mol) was added dropwise to 50 mL of a solution of 2,4-dinitrofluorobenzene (Sanger's Reagent, 99%, Aldrich, 10 g, 54 mmol) and triethylamine (99+%, Aldrich, 10 g, 99 mmol) in dry chloroform in a three-necked flask equipped with magnet stirrer and nitrogen inlet-outlet. The reactor was stirred overnight under nitrogen blanket. The color of the solution changed from orange to dark red. The solution was extracted with 1M HCl and repeatedly with water. The organic phase was separated and filtered to yield yellow crystals which were repeatedly recrystallized from chloroform. Yield was 91%, M 170.5° C. and was characterized by ¹H-NMR.

The poloxamer was then treated with the protected thiol to obtain the end-activated compound shown in equation (4).



Diisopropyl azodicarboxylate (95%, Aldrich, 5 g, 25 mmol) was added to a stirred solution of Pluronic F127 NF (54.4 g, 8 meq OH groups) and triphenylphosphine (99%, Aldrich, 6.5 g, 25 mmol) in 30 mL of dry tetrahydrofuran (THF). Prior to use, the poloxamer was lyophilized to remove water traces. The solution was then stirred for 48 h at ambient temperature under a nitrogen blanket. Then the solution was precipitated into chilled methanol/hexane (2:1), dried, redissolved in THF and repeatedly precipitated by hexane. After filtering and drying under vacuum, the yield 88%.

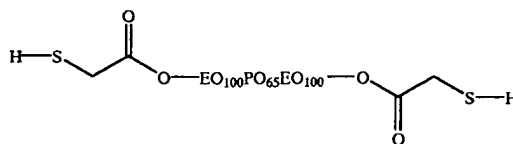
The protected-thiol functionalized poloxamer was then deprotected to obtain the reactive thiol according to equation (5).



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Poloxamer functionalized with protected thiol (20 g) was dissolved in dry THF (100 mL) and 2-mercaptoethanol (98%, Aldrich, 5 g). Triethylamine (10 g) was added to the solution dropwise and the mixture was stirred at ambient temperature for 16 h. The resulting mixture was precipitated into chilled methanol/hexane (2:1), dried, redissolved in THF and repeatedly precipitated by hexane. After filtering and drying of the resulting polymer under vacuum, the yield was 90%.

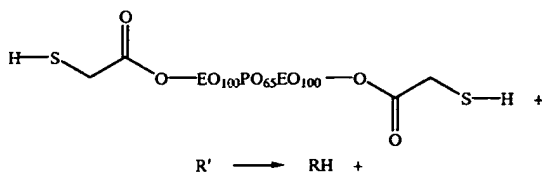
The thiol-functionalized poloxamer of the preceding step was then dissolved in acrylic acid (99%, Aldrich, 5 g) and the solution was charged into a 100 mL multinecked, thermostated flanged glass reactor equipped with a mechanical stirrer, syringe sampler, thermometer, programmable heater bath, and a gas inlet/outlet. The reactor was charged with 50 mL of 1% poly(vinyl alcohol) (99% hydrolyzed, MW 13,000, Aldrich) solution in dodecane and was deoxygenated for 2 h by nitrogen flow while stirring. A freshly prepared initiator system comprising 1 mL of freshly prepared ammonium persulfate (Aldrich, 99.9+%; 30 mg) and N,N,N',N'-tetramethylethylenediamine (Aldrich, 99.5%; 0.2 mL) in water/acrylic acid mixture was added into the solution of poloxamer in acrylic acid while stirring. The solution was equilibrated for 24 h at 30° C. under nitrogen purge introduced from the bottom of the reactor. The reactor was allowed to equilibrate at ambient temperature, the nitrogen flow was discontinued and the slurry of the resulting polymer was filtered off using Whatman filter paper (retention 10 μ m). The polymer was repeatedly washed with excess heptane and then with excess hexane in a separation funnel. The resultant white powder (poloxamer end-modified with poly(acrylic acid)) was dried under vacuum at 40° C. for 24 h.

The resulting copolymer was characterized by NMR and IR as follows.

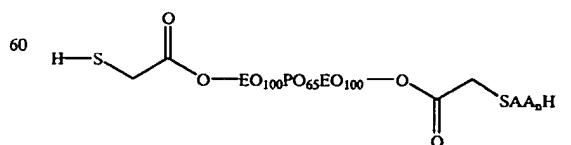
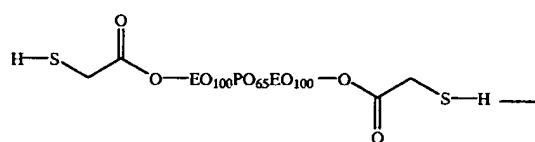
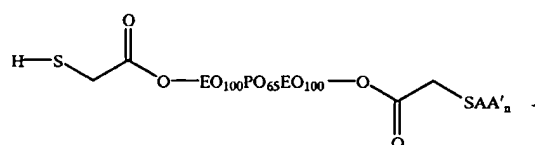
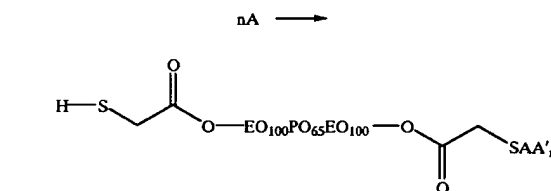
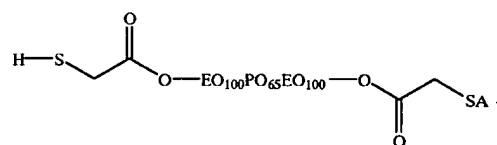
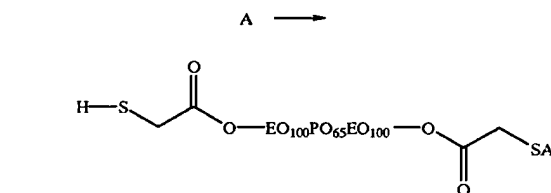
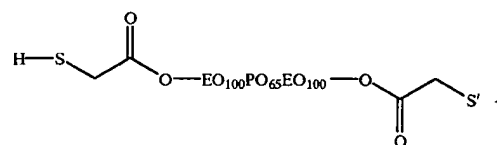
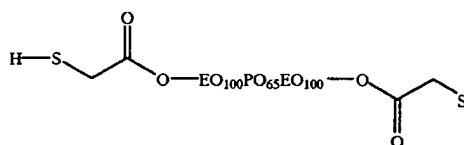
^{13}C -NMR (D_2O , 20° C., 10%): δ 177 (ester COOH), 76–70 (ether C—O—C), 66 (C—S), 46–37 (primary C—O and secondary C—C), 17.9 (CH_3 of PPO).

IR (KBR): 2945 (methyl CH of PPO), 1743 ($\text{C}=\text{O}$), 1220 (ester C—O stretch), 1099 (antisym and sym COC stretch) cm^{-1} .

Gel-permeation chromatography was run as described in Example 2. Number-weight, z-average molar masses for the copolymer were found to be 1.30×10^5 , 1.35×10^5 and 1.39×10^5 , respectively. The very narrow molecular weight distribution agrees well with the chain-transfer mechanism of polymerization which is shown in Scheme 1.

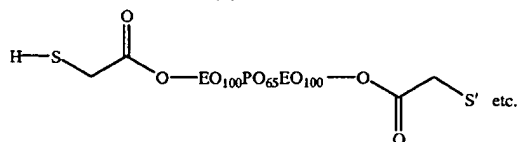


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The material was evaluated for thermal-responsiveness. The results are reported in FIG. 6. Viscosity in equilibrium flow experiments of an 8% aqueous solution (pH 7.0) indicates that the solution viscosity at body temperature. The steady-shear viscosity that is higher by many orders of magnitude at body temperature than at ambient confirms the gelation process.

EXAMPLE 7

The following examples provide exemplary formulations for the pharmaceutical and cosmetic applications of the invention.

Aceclofenac Gel (1.5%). An example of a gel containing Acceclofenac as the active agent.

Acceclofenac	1.5 g
Miglyol ® 812 (Dynamit-Nobel)	9.9 g
Water	qs
Hydrogel of the invention	3.0 g

Mix the Acceclofenc and Miglyol with water and cool to about 5° C. Add slowly Hydrogel and continue stirring until the hydrogel is dissolved. Maintain cooling until the air bubbles escape. A milky gel is obtained. When heated to body temperature the gel firms.

Lidocain Gel (2%). An example of a topical gel containing Lidocaine as the active agent.

Lidocain hydrochloride	2 g
Water	58 g
Propylene glycol	20 g
Hydrogel of the invention, solution 10% w/w	20 g

Prepare solution of Lidocain and propylene glycol in water at room temperature, cool to about 5° C. and add slowly Hydrogel solution to the well-stirred solution until it is homogenized. Maintain the temperature until the air bubbles escaped. A clear colorless gel is obtained. The product is liquid at room temperature and becomes firm gel at body temperature to allow precise application and residence.

Carbonate Dry Syrup (12.5%+12.5%) (Aluminum Hydroxide+Magnesium). An example of anti-acid esophageal preparation is provided. Granulate the following ingredients.

Aluminum hydroxide dry gel	25.0 g
Basic Magnesium carbonate	25.0 g
Kollidon CL-M	29.0 g
Sorbitol, crystalline	25.6 g
Orange flavor	5.0 g

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Prepare the following solution:

Kollidon 30	10.0 g
Coconut flavor	0.4 g
Banana flavor	0.5 g
Saccharin sodium	0.5 g
Water	0.1 g

Mix the granulates with the solution and pass through a sieve and air dry. Shake 60 g of the resulting powder with 100 ml of water containing 3 wt % inventive Hydrogel. This solution will coat the esophagus to provide relief from GERD.

Diltiazem Tablets. An example for sustained release tablet.

Diltiazem	60 g
Ludipress (BASF)	130 g
Polyethylene glycol 6000	5 g
Aerosil 200	1 g
Magnesium stearate	1 g
Hydrogel of the invention, powder	10 g

Mix all components, pass through a sieve and press with low compression force. This tablet will have a sustain release characteristics due to the slow dissolution of the Hydrogel at body temperature.

Beta Carotene Effervescent Tablets. An example for sustained release effervescent tablet.

Lucarotin ® powder (BASF)	70 g
Ludipress	113 g
Citric acid, anhydrous	200 g
Sodium bicarbonate	120 g
Sodium carbonate	12 g
Sodium cyclamate	20 g
Aspartame	15 g
Orange flavor	20 g
Polyethylene glycol 6000, powder	20 g
Hydrogel of the invention, powder	10 g

Pass all components through a 0.8 mm sieve, mix and press with medium or high compression force at maximum 30% of relative atmospheric humidity.

Chlorhexidine Gel (2%). A formulation to be used in the oral cavity with longer residence time

Chlorhexidin diacetate	2 g
1,2-Propylene glycol	30 g
Hydrogel of the invention, powder	2 g
Pluronic F127, powder	2 g
Water	qs

Dissolve chlorhexidin diacetate in propylene glycol at >70° C., add water under stirring. Cool to about 5° C. and add the inventive Hydrogel and F127. Stir until dissolved. Maintain the temperature until the air bubbles escaped. A clear colorless gel is obtained.

Aloe Vera Gel. An example for a cosmetic formulation.

Aloe vera extract	0.4 g
Propylene glycol	5.0 g

-continued

Preservative	q.s.
Water	73.6 g
Cremophor RH 40 [1]	1.1 g
Perfume	q.s.
Hydrogel of the invention, powder	3.0 g

Prepare the solutions containing all ingredients but the responsive Hydrogel. Cool this mixture to about 5° C. and dissolve the inventive Hydrogel. Maintain the temperature until the air bubbles escaped. The formed hydrogel is clear and flowable at room temperature. Once applied on the skin the solution viscosity to provide a cushion and lubricious effect.

Hydrocortisone Aqueous Gels (1%). Hydrophobic substances is solubilized by Hydrogel of the invention.

Hydrocortisone acetate	1.0 g
Hydrogel of the invention	4.0 g
Carbopol 940 (Goodrich)	0.5 g
Water	qs
Preservative	q.s.
Triethanolamine 10% solution	8 g

Dissolve the inventive hydrogel in cold water (5° C.). Add the Carbopol, and mix until the solution is clear. Suspend the hydrocortisone and allow it to dissolve at room temperature, under gentle stirring overnight. Add a solution of triethanolamine and continue to stir until the gel is clear.

Metronidazol Vaginal Gel (1.2%). An example for a vaginal formulation.

Metronidazol	1.2 g
Pluronic F 127	2.0 g
Hydrogel of the invention	3.0 g
Water	qs g

Mix all the above ingredients at 5° C. until dissolved. Maintain the temperature until the air bubbles disappeared.

Vitamin E Gel-Cream (10%). An example for a cosmeceutical formulation of a semi-solid gel.

Vitamin E acetate (BASF)	10 g
Propylene glycol	15 g
Hydrogel of the invention	5 g
Pluronic F127	3 g
Water	qs

Mix vitamin E acetate with propylene glycol and add the water. After cooling to about 5° C. dissolve slowly the Hydrogel in the well stirred mixture. Maintain cool until the air bubbles escaped. The inventive Hydrogel provide a solublizer for the Vitamin E and provides the "body" of the formulation.

What is claimed is:

1. A reverse thermally viscosifying composition comprising:

a linear block copolymer comprising:

at least a first polyoxyalkylene block having a hydrophobic region and a hydrophilic region effective to form micelles in solution in response to a change in temperature, and

at least a second block comprising a bioadhesive polymer or oligomer,

wherein the linear block copolymer is dispersed in an aqueous medium and the composition reversibly viscosifiers at a temperature in the range of 22 to 40° C.

2. The composition of claim 1, wherein said polyoxyalkylene comprises polyoxyethylene as the hydrophilic region and polyoxypropylene as the hydrophobic region.

3. The composition of claim 1, wherein said polyoxyalkylene comprises an alkyl poloxamer of the formula, $R-(CH_2CH_2)_nO-$, where R is an alkylene or arylalkylene moiety and n is in the range of 5 to 100.

4. The composition of claim 1, wherein the bioadhesive polymer or oligomer is a mucoadhesive.

5. The composition of claim 1, wherein the bioadhesive polymer or oligomer comprises a poly(vinylcarboxylic acid).

6. The composition of claim 5, wherein the poly(vinylcarboxylic acid) is selected from the group consisting of acrylic acid, substituted acrylic acids, methacrylic acid, substituted methacrylic acids, and ionized forms thereof.

7. The composition of claim 1, wherein the polyoxyalkylene comprises a triblock polymer of polyoxyethylene (POE) and polyoxypropylene (POP) having the formula $(POE)_a(POP)_b(POE)_c$, where a is in the range of 100-50, and b is in the range of 50-70.

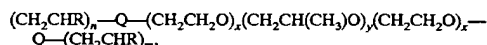
8. The composition of claim 1, wherein the viscosification occurs at a temperature in the range of about 30 to 37° C.

9. A block copolymer or oligomer, comprising:

at least one polymer or oligomer block including a polyoxyalkylene having a hydrophobic region and a hydrophilic region in a proportion effective to form micelles in solution in response to a change in temperature; and

at least one block comprises a bioadhesive polymer or oligomer, wherein said block polymer is a linear block copolymer.

10. The block copolymer of claim 9, having the formula



where Q is selected from the group consisting of C—C, C—O, C(O)NH, S—C, C(O)—O functionality, R is a carboxyl, and n, m, x, and y are independently selected and in the range of 1 to 1000.

11. A pharmaceutical composition, comprising:

a reverse thermally viscosifying composition including a linear block copolymer, wherein at least one block comprises a poloxamer having a hydrophobic region and a hydrophilic region effective to form micelles in solution in response to a change in temperature; and at least one block comprises a bioadhesive polymer or oligomer, in an aqueous medium; and

an active agent which imparts a pharmaceutical or cosmetic effect, wherein the composition reversibly viscosifiers at a temperature in the range of 22 to 40° C.

12. The composition of claim 1 or 11, wherein the block copolymer is present in an amount in the range of about 0.01 to 20 wt % of the reversible viscosifying composition.

13. The composition of claim 1 or 11, wherein the block copolymer is present in an amount in the range of about 0.1 to 10 wt % of the reversible viscosifying composition.

14. The composition of claim 1 or 11, wherein the block copolymer is present in an amount in the range of about 0.01 to 1 wt % of the reversible viscosifying composition.

15. The pharmaceutical composition of claim 11, wherein said composition further comprises a pharmaceutical agent selected from the group consisting of humectants and emollients.

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16. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition takes a form selected from the group consisting of lotions, creams, sticks, roll-on formulations, sprays, aerosols, pad-applied formulations and masks.

17. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through skin or mucosal membranes.

18. The composition of claim 1 or 11, wherein the aqueous-based medium is selected from the group consisting of water, salt solutions and water with water-miscible organic compound(s).

19. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through vaginal mucosal membrane.

20. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through nasal mucosal membrane.

21. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through rectal mucosal membrane.

22. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through otic mucosal membrane.

23. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through ophthalmic mucosal membrane.

24. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through esophageal mucosal membrane.

25. The pharmaceutical composition of claim 11, wherein the pharmaceutical agent is absorbable through oral cavity membrane.

26. The pharmaceutical composition of claim 22, wherein the pharmaceutically active agent is selected from the group consisting of miotics, sympathomimetics, beta-blockers, prostaglandins, muscarinic antagonists, anti-infectives, and carbonic anhydrase inhibitors.

27. The pharmaceutical composition of claim 11, further comprising acceptable antioxidants.

28. The pharmaceutical composition of claim 11, further comprising isotonicizing agents.

29. The pharmaceutical composition of claim 11, further comprising a buffer.

30. The pharmaceutical composition of claim 11, further comprising preservative.

31. The pharmaceutical composition of claim 19, wherein the pharmaceutically active agent is selected from the group consisting of natural and synthetic hormones, antifungals, contraceptives, anti-yeast agents, steroids, moisturizers, spermicides, anti-virals, analgesics and anesthetics.

32. The pharmaceutical composition of claim 11, wherein the pharmaceutically active agent is selected from the group consisting of anti-ulcer agents, sucralfate, H2-blocking

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agents, antipyretics, analgesics, antacids, antiflatulents, anticonvulsants, antidiarrheals, antifungals, antihypertensives, antihistamines, antipruritics, anti-infectives, antinauseants, antireflux agents, antispasmodics, contraceptives, hormonal, steroids, cough/cold remedies, diuretics, laxatives, tranquilizers, muscle relaxants, mineral supplements, sedatives, vitamins and mixtures thereof.

33. The pharmaceutical composition of claim 32, further comprising flavoring.

34. The pharmaceutical composition of claim 20 or 22, wherein the pharmaceutical composition is applied in the form of drops.

35. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition is applied as a spray.

36. The pharmaceutical composition of claim 20, wherein the pharmaceutically active agent is selected from the group consisting of decongestants, antihistamines, anti-osteoporosis agents, hormones, antineoplastic agents, Parkinsonism drugs and vaccines.

37. The pharmaceutical composition of claim 11, wherein the reversible thermal viscosifying composition is incorporated into a tablet for oral administration.

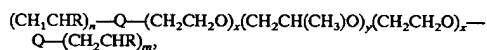
38. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is injectable.

39. The pharmaceutical composition of claim 15, wherein the pharmaceutically active agent is selected from the group consisting of anti-ulcer agents, sucralfate, H2-blocking agents, antipyretics, analgesics, antacids, antiflatulents, anticonvulsants, antidiarrheals, antifungals, antihypertensives, antihistamines, antipruritics, anti-infectives, antinauseants, antireflux agents, antispasmodics, contraceptives, hormonal, steroids, cough/cold remedies, diuretics, laxatives, tranquilizers, muscle relaxants, mineral supplements, sedatives, vitamins and mixtures thereof; and

further comprising flavoring.

40. The composition of claim 1 or 11, wherein the polyoxyalkylene comprises a triblock polymer of polyoxyethylene (POE) and polyoxypropylene (POP) having the formula $(POE)_a(POP)_b(POE)_c$, where a is 100, and b is 65.

41. The composition of claim 1 or 11, wherein the linear block copolymer has the formula,



where Q is selected from the group consisting of C—C, C—O, C(O)NH, S—C, C(O)—O functionality, R is a carboxyl, and n, m, x, and y are independently selected and in the range of 1 to 1000.

* * * * *

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App. Serial No. 10/788,277

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

ROSENTHAL et al.

Serial No.: 10/728,277

Filed: December 4, 2003

Conf. No.: 7142

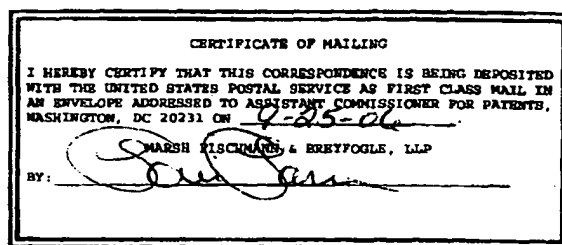
Atty. File No.: 42830-10010

For: "TREATMENT OF MUCOSITIS"

Group Art Unit: 1614

Examiner: Roberts, Lezah

RULE 132 DECLARATION
OF JANICE M. TROHA
(37 C.F.R. § 1.132)



Assistant Commissioner for Patents
Washington, D.C. 20231

I, Janice M. Troha, residing at 7394 Cortez Lane, Boulder, CO 80303, declare as follows:

Qualifications And Basis For Declaration:

I am currently employed in the capacity of Vice President, Clinical Development Regulatory Affairs at RxKinetix, Inc. ("RxKinetix"), the assignee of referenced U.S. Patent Application No. 10/728,277 (the "Pending Application"). In my current position, I have worked extensively, and gained considerable experience in the area of oral mucositis as a side effect of cancer therapy.

The attached Exhibit A is a summary of my technical qualifications.

The attached Exhibit B includes tabular data from an animal study in hamsters concerning the use of N-acetylcysteine ("NAC") for the treatment of radiation-induced oral mucositis.

I have reviewed and considered the Pending Application, including pending claims, and an Office Action dated March 23, 2006 issued by the United States Patent and Trademark Office on March 23, 2006 (the "Office Action") concerning the Pending Application.

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I have reviewed and considered U.S. Patent Number 5,358,705 by Boggs et al. ("Boggs et al.") and U.S. Patent Number 6,503,955 by Dobrozsi et al. ("Dobrozsi et al."), which have been cited by the patent Examiner in the Office Action.

Mucositis:

Oral mucositis has long been recognized as a common and often debilitating side effect of cancer therapy. In patients with head and neck cancer who receive high doses of radiation as part of their cancer treatment the incidence of severe mucositis is high. Furthermore, there is no treatment for oral mucositis that is currently approved by the United States Food and Drug Administration for use in these patients. Oral mucositis begins in the endothelial layer of the oral mucosa, or endothelium. The oral mucosa is comprised of three distinct layers, the first being the epithelial layer or outer surface of the mucosa, the second layer is the lamina propria and the third and deepest layer of the oral mucosa is the endothelium, also referred to as the submucosa. Chemotherapy and radiotherapy initiate inflammatory changes that begin in the endothelial layer of the oral mucosa. These changes then set up a cascade of events that extend to the epithelium and the surface of the oral cavity tissues. At first these changes appear as reddened inflamed tissue and, eventually, as ulcers. These ulcers may be superficial or deep and necrotic depending on the severity of the disease. Bacteria are not involved in the initial stages of oral mucositis. The presence of bacteria in the oral cavity may complicate the progression of mucositis and the healing process, once ulcers have developed, but they are not a causative factor. Antibacterial agents have been tested in patients with oral mucositis, but I am not aware of any antibacterial agent that has been found to be effective for treating oral mucositis, further refuting any role for bacteria as a causative factor in the pathogenesis of oral mucositis. Development of mucositis at other locations in the body as a side effect of cancer therapy would be mechanistically similar to that described above for oral mucositis. The discussion here focuses on oral mucositis, but the same general principles apply to mucositis occurring at other locations.

The World Health Organization ("WHO") and the National Cancer Institute ("NCI") have each developed scales for assessing the severity of oral mucositis resulting from cancer therapy, with a greater score on each scale indicating a more severe form of oral mucositis. Although a desirable treatment for oral mucositis would result in lower overall oral mucositis

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scores by patients, it is particularly desirable that the treatment reduces the number of patients developing severe oral mucositis. Severe oral mucositis is indicated by a score of 3 or greater on the WHO or NCI oral mucositis toxicity scales. The progression from a score of 2 to a score of 3 is highly clinically significant, even though there is only one incremental point difference between the scores.

A score of 2 on the WHO or NCI scales represents moderate oral mucositis. Patients developing such moderate oral mucositis may require aggressive pain management but they are able to maintain adequate oral intake and do not normally require aggressive clinical interventions, such as feeding tubes, cessation of cancer treatment and/or hospitalization. As noted above, a score of 3 or greater is considered severe oral mucositis. Severe oral mucositis often develops in cancer therapy patients undergoing radiation therapy and/or chemotherapy, and development of such severe oral mucositis causes significant morbidity, which can seriously complicate continuance of the cancer therapy. Consequences of developing severe oral mucositis may include prescription of opiate analgesia for pain management, insertion of an external feeding tube for maintenance of adequate nutrition, hospitalization to manage symptoms, and systemic infection. Other consequences of developing severe mucositis may include reduction in doses of chemotherapeutic agents or radiation and delays or even complete discontinuation of radiation therapy or chemotherapy. Such alteration of the cancer treatment regimen adversely impacts curability. The possibility for successful completion of cancer therapy is significantly negatively impacted by the occurrence of severe oral mucositis and there has been and continues to be a significant need for oral mucositis treatments, and especially for a treatment that reduces the incidence of severe oral mucositis in cancer therapy patients.

Dobrozsi et al. and Boggs et al. References:

Dobrozsi et al. describe their invention as directed to pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments (column 3, lines 2-4). The pourable liquid vehicle is such that as the vehicle acquires moisture during use, the vehicle transforms from a liquid to a gel-like form (column 1, lines 14-16; column 3, lines 36-47; column 4, lines 33-48). Dobrozsi et al. provide a long listing of possible substances that could be delivered using the pourable liquid vehicle (column 7, line 26 through column 9, line 27), and as one possibility mention "Expectorants/Mucolytics" including, among

other things, NAC. Expectorants and mucolytics are agents used to breakdown and expel mucous from the respiratory tract. The disclosed possible use of NAC as an expectorant or mucolytic is not indicative of efficacy for the treatment of oral mucositis, and the disclosure of Dobrozsi et al. would not lead to an expectation, nor predict that NAC has efficacy for the treatment of oral mucositis. The demonstration of efficacy as an expectorant or mucolytic, to remove material from the surface of the mucosal membrane is entirely unrelated to the condition of oral mucositis and would not be indicative of efficacy to treat a condition such as oral mucositis, which develops beginning in the endothelial layer of the oral mucosa, as discussed above.

Boggs et al. describe their invention as being directed to compositions for reducing or preventing dental plaque, or gingival or periodontal diseases, of the oral cavity in humans or lower animals (column 1, lines 44-51). According to Boggs et al., toxins in plaque and calculus (a hard crusty deposit on teeth that can develop from plaque) can irritate the gingival tissues surrounding teeth coated with the plaque or calculus, causing inflammation and destruction of the gums (column 1, lines 29-39). The compositions of Boggs et al. include as an active ingredient a complex of certain metal ions with N-acetylated amino acids (column 1, lines 44-58). Boggs et al. list NAC as being one possibility for the N-acetylated amino acid for use in the active ingredient complex (column 2, line 65 through column 3, line 2). Boggs et al. note that mechanistically, the use of the active ingredient complex leads to a dramatic reduction in bacteria binding to the tooth surface, and because bacteria are impeded from adhering to the teeth, fewer bacteria are present on the tooth surface to multiply, with the result that there is a reduction in the bacterial accumulation, and consequently a reduction in plaque and gingivitis (column 3, lines 34-40 and 54-58).

The disclosure by Boggs et al. would not lead to an expectation, nor predict that NAC has efficacy for the treatment of oral mucositis. The mechanism for action described by Boggs et al. concerning reductions in bacterial binding to the tooth is not indicative of efficacy in relation to the treatment of oral mucositis, the pathogenesis of which does not appear to be due to the presence of bacteria. Moreover, as discussed above, oral mucositis begins in the endothelial layer of the oral mucosa, and not at the superficial level of the surface of the gum or tooth, which is the area of interest to Boggs et al.

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Animal Study On Use Of NAC To Treat Oral Mucositis:

The EXAMPLE presented on pages 24-27 of the Pending Application discusses an animal study conducted in hamsters concerning the use of NAC as an active agent to treat oral mucositis resulting from irradiation. In the study (the details of which are discussed more fully in the Pending Application), oral mucositis was induced in hamsters through targeted irradiation of the left buccal pouch with a total of 40 Gy of radiation on day 0. For 28 days post-irradiation, the hamsters were dosed topically in the oral cavity 3 times per day with either a treatment formulation containing NAC or a control formulation not containing NAC. Compositions of treatment and control formulations are shown in Table 1 of the Pending Application, and the compositions of the control formulations and two selected treatment formulations are repeated in Table D-1 below, for convenience in relation to the discussion provided below.

Table D-1. Compositions Of Selected Test Formulations Used In Animal Study

Formulation	NAC (Wt %)	Poloxamer 407 ¹ (Wt %)	Chitosan (Wt %)	NaOH (M)	pH
N-acetylcysteine Formulations					
A2.02	10	16.25	0	0.57	4-5
A2.03	10	0	0	0.57	5-6
CONTROL FORMULATIONS					
Vehicle control	0	16.25	0.5	0	5-6
Water control	0	0	0	0	

¹ Pluronic® F-127

Beginning on day 6 post-irradiation and continuing every second day thereafter through day 28, mucositis was preliminarily scored by an investigator upon examining the buccal pouch and using a validated photographic scale ranging from 0 for normal to 5 for maximum ulceration. A score of 3 or greater is considered to correspond with development of severe oral mucositis. The results of this preliminary scoring in terms of average mucositis score are shown graphically in Figure 1 of the Pending Application, which is not repeated here. A description of the scoring used in the hamster study is presented in Table 2 of the Pending Application. This scoring scale was developed for use in animal studies to approximate the severity of oral mucositis that would be indicated by the corresponding score on the NCI or WHO scales for

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human patients. Table D-2 below provides a comparison between the oral mucositis scoring scale used in the animal study and the NCI oral mucositis scale.

Table D-2. Oral Mucositis Toxicity Scales Comparison

Score	Mucositis Toxicity Scale Used in Animal Study	NCI Toxicity Scale Used in Patients
0	No mucositis	No mucositis
1	Light to severe erythema and vasodilation No erosion of the mucosa	Erythema of the mucosa (of any severity)
2	Severe erythema and vasodilation. Erosion of superficial aspects of mucosa leaving denuded areas. Decreased stippling of mucosa.	Patchy ulcerations or pseudomembranes (patches generally ≤ 1.5 cm in diameter and non-contiguous)
3	Formation of off-white ulcers in one or more places. Ulcers may be yellow/gray due to pseudomembrane. Cumulative size of ulcers should equal about 25% of the pouch ¹ . Severe erythema and vasodilation	Confluent ulcerations or pseudomembranes (contiguous patches generally > 1.5 cm in diameter)
4	Cumulative size of ulcers should equal about 50% of the pouch. Loss of pliability (pouch can only be partially extracted from the mouth).	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences.
5	Virtually all of the pouch is ulcerated. Loss of pliability (pouch can only partially be extracted from the mouth)	Death

¹ Refers to hamster cheek pouch

In addition to the preliminary scoring, beginning on day 6 post-irradiation and continuing every second day thereafter, photographs were taken of the buccal pouch of the hamsters. The photographs were subsequently reviewed in blinded fashion by two investigators who each scored oral mucositis as revealed by the photographs, using the same photograph validated scale developed for animal studies, as noted above and summarized in Table D-2. The preliminary scoring provided a good real time indication of mucositis development in the hamsters during the study, but the blinded photographic scoring is considered to be better controlled and more verifiable than the preliminary scoring. Exhibit B contains a tabulation of oral mucositis scores assigned by the investigators in the blind photograph scoring of hamster groups for each of the test formulations shown in Table D-1 above.

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In the blinded scoring, if an animal receives a score of 3 or greater from either investigator on any given day, then that animal is considered to have severe oral mucositis on that day. Table D-3 below summarizes the number and percentage of scoring days for all animals (referred to as animal-days) in each treatment group on which a score of 3 or greater was assigned by either investigator, indicating severe mucositis.

Table D-3. Animal-Days Scored With Severe Mucositis

	Water Control	Vehicle Control	RK-0203	RK-0202
Total Number Animal-Days	84	84	72	72
Number Animal-Days With Severe Mucositis Score	51	36	15	3
% Animal-Days With Severe Mucositis Score	61%	43%	21%	4%

For the RK-0203 formulation (NAC in water), the lower prevalence of severe mucositis scores (only 21%) is very significant in comparison to the water control formulation (61%), indicating that NAC has significant efficacy in the treatment of oral mucositis. This would not be expected based on the quite different uses for NAC described in the Dobrozsi et al. and Boggs et al. references cited in the Office Action, as discussed above. The results shown in Table D-3 for RK-0202 are particularly striking, with only 4% of the scored animal-days showing severe mucositis scores. Even if NAC had been previously known as being effective for treatment of oral mucositis, this result is very significant and would not be expected based solely on the change in delivery formulation between RK-0203 (NAC in water) and RK-0202 (reverse-thermal gelling composition with poloxamer 407).

It is noted that, as shown in Table D-3, the vehicle control formulation (poloxamer 407, chitosan and water, with no NAC) had a lower incidence of severe mucositis on scored days than the water control formulation (no poloxamer 407 or NAC). Although this result for the vehicle control formulation is interesting, on closer examination of the data presented in Exhibit B it is of only limited, if any, significance in a clinical context concerning treatment for oral mucositis in human patients undergoing cancer therapy.

When human patients undergoing cancer therapy develop severe oral mucositis, it is a development that is detrimental to continuation of the cancer therapy, and calls for immediate attention. The cancer therapy will typically involve multiple radiation and/or chemotherapeutic doses given at periodic intervals. The human patient does not have the benefit of a significant

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recovery period between doses, and the next cancer treatment dose is an aggravating event for oral mucositis that has already developed. From a clinical perspective, considering human patients undergoing cancer therapy, the number of animals in each study group that developed severe mucositis at some time during the animal study is highly relevant, whether or not oral mucositis scores thereafter decreased during the animal study.

Table D-4 summarizes data from Exhibit B concerning the incidence, by test group, of animals receiving an oral mucositis score indicative of severe oral mucositis at some time during the animal study. An animal is considered to have developed severe oral mucositis if the animal reached a score of 3 or greater from either investigator on any day scored during the study.

As seen in Table D-4, by day 16 all of the animals in the water control and vehicle control groups had reached a severe oral mucositis score. For RK-0203, 5/6 or 83% of the animals reached a severe oral mucositis score, and attainment of that level occurred on day 18. Strikingly, only 2/6 or 33% of the animals in the RK-0202 group reached a severe oral mucositis score. Also significant for RK-0202 is that no animal in that group received a severe mucositis score until day 14, later than any of the other groups. This apparent delay in the onset of severe mucositis and lower overall number of animals reaching a severe mucositis score for the RK-0202 group is very significant and surprising, and especially so in comparison to the RK-0203 group, which received the same amount of the NAC active ingredient. The significant reduction in the total number of animals receiving a severe oral mucositis score using RK-0202 compared to RK-0203 would not be expected due simply to the change in the delivery vehicle (reverse-thermal gelling composition with poloxamer 407 vs water).

Table D-4. Animals Developing Severe Mucositis During Study

	Water Control	Vehicle Control	RK-0203	RK-0202
Fraction Animals That Developed Severe Mucositis				
Through Day 6	0/7	0/7	0/6	0/6
Through Day 8	0/7	0/7	1/6	0/6
Through Day 10	1/7	0/7	1/6	0/6
Through Day 12	4/7	2/7	3/6	0/6
Through Day 14	5/7	6/7	3/6	1/6
Through Day 16	7/7	7/7	4/6	1/6
Through Day 18	7/7	7/7	5/6	1/6
Through Day 20	7/7	7/7	5/6	2/6
Through Day 22	7/7	7/7	5/6	2/6
Through Day 24	7/7	7/7	5/6	2/6
Through Day 26	7/7	7/7	5/6	2/6
Through Day 28	7/7	7/7	5/6	2/6
% Animals That Developed Severe Mucositis				
Through Day 6	0%	0%	0%	0%
Through Day 8	0%	0%	17%	0%
Through Day 10	14%	0%	17%	0%
Through Day 12	57%	29%	50%	0%
Through Day 14	71%	86%	50%	17%
Through Day 16	100%	100%	67%	17%
Through Day 18	100%	100%	83%	17%
Through Day 20	100%	100%	83%	33%
Through Day 22	100%	100%	83%	33%
Through Day 24	100%	100%	83%	33%
Through Day 26	100%	100%	83%	33%
Through Day 28	100%	100%	83%	33%

Phase 2 Clinical Trial:

A phase 2, prospective, randomized, placebo-controlled, double-blind study was conducted to compare the effect of two treatment formulations (Formulation 1 containing 5% NAC and Formulation 2 containing 10% NAC) with placebo on the incidence of severe oral mucositis in human patients treated with radiation therapy (RT) for head and neck cancer. Each of the treatment formulations contained sufficient poloxamer 407 (Pluronic® F-127) to impart reverse-thermal gelation properties to the test formulations. The compositions of the test formulations are summarized in Table D-5 below.

Table D-5 Compositions of Treatment Formulations

Component	Formulation 1 (5% NAC)	Formulation 2 (10% NAC)
	% (w/w)	% (w/w)
NAC	5.00	10.00
Poloxamer 407 ¹	13.00	13.00
Calcium Sodium EDTA	0.09	0.09
Methyl Paraben	0.20	0.20
Sodium Citrate	0.29	0.29
Sodium Hydroxide	1.225	2.450
Sterile Water	77.70	71.50
Sucralose	0.050	0.050
Pure Lemon Extract	2.40	2.40

¹ Pluronic® F-127 or Lutrol® F-127

The study was conducted at 15 sites in North America (12 in the US; 3 in Canada). The protocol was approved by the institutional or ethics review board at each site. All patients gave written informed consent before entry and before study related procedures were performed. Eligible patients had confirmed cancers of the oral cavity, oropharynx, nasopharynx or salivary glands; were at least 18 years of age; had a Karnofsky performance status of at least 60 and were scheduled to receive at least 60 Gy of RT. The planned volume had to include at least 3 oral qualifying sites, defined as one that would receive at least 60 Gy to 2 cm². RT could consist of 1.8 to 2.2 Gy per day in single fractions and up to 3.3 Gy during concurrent boost. Patients were excluded from the study if they were to receive concomitant chemotherapy, amifostine or pilocarpine, or if they had evidence of oral mucositis at baseline, prior RT to the head and neck, or hypopharyngeal tumors. Patients with a medical or sociological, or psychological impairment

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that would likely affect their compliance with the protocol were also excluded. Concomitant use of oral antifungals, topical and systemic analgesics as well as palliative mouth rinses consisting of viscous lidocaine, milk of magnesia, baking soda and salt were allowed. A standard, oral care protocol was followed at each institution. Patients were instructed to brush their teeth twice daily, floss once daily, apply fluoride treatments and refrain from wearing dentures. Commercial mouthwashes were prohibited. Patients rinsed with the treatment formulation or placebo 6 times daily during their RT. The 5% NAC dosage strength treatment formulation (Formulation 1) was eliminated at interim analysis by an Independent Data Monitoring Committee due to a lower effect compared with the 10% NAC dosage strength treatment formulation (Formulation 2). The primary comparison was, therefore, between Formulation 2 and placebo in the intent-to-treat population. Analyses of all efficacy and safety endpoints included all qualifying patients who underwent randomization and received at least one dose of study drug. The efficacy of the treatment formulations was assessed by evaluating the incidence of grade ≥ 3 oral mucositis, by a cumulative dose of 60 Gy of radiation, using both the WHO and NCI toxicity scales. The data was analyzed using a time-to-failure approach, with cumulative RT dose substituted for time, and the interval specified as 0 to 60 Gy. Patients with WHO or NCI grade 0, 1, or 2 oral mucositis were defined as successes and those with a grade ≥ 3 as failures. Any patient that reached a WHO or NCI score of 3 was carried forward as a failure throughout RT regardless of whether they subsequently discontinued treatment or returned to a lower score. Efficacy was also assessed by evaluating the need for opiate analgesia and surgically placed feeding tubes. Table D-6 summarizes the WHO and NCI oral mucositis toxicity scales that were used.

Table D-6. WHO and NCI Oral Mucositis Toxicity Scales

Score	Description	
	WHO Toxicity Scale	NCI Toxicity Scale
0	None	None
1	Soreness and erythema	Erythema of the mucosa (of any severity)
2	Erythema, ulcers, maintains ability to eat solids	Patchy ulcerations or pseudomembranes (patches generally ≤ 1.5 cm in diameter and non-contiguous)
3	Ulcers, requires liquid diet	Confluent ulcerations or pseudomembranes (contiguous patches generally > 1.5 cm in diameter)
4	Ulceration present, alimentation not possible	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences.
5	NA	Death

As shown in the table below, the baseline demographic and disease characteristics of the patients were generally similar among the groups (Table D-7). Compliance was good with a mean number of daily doses of 5.1 out of 6, and 80% of patients rating the study drug as acceptable.

Table D-7. Baseline Patient Characteristics

Group Number	Formulation 2 38	Placebo 29
Age-mean (sd)	58 (14)	59 (14)
Median	56	58
Gender -- % males	61%	69%
Smoking Pack Years -- Mean (sd)	24.2 (21.4)	31.8 (38.7)
Median	16.8	20
Current Smokers -- Number (%)	4 (11%)	4 (14%)
Drinks Per Day -- Mean (sd)	2.6 (2.71)	1.7 (2.01)
Median	1.5	1
Current Drinkers -- Number (%)	17 (45%)	11 (38%)
Planned RT in Gy		
Total Dose -- Mean (sd)	64.2 (4.9)	64.2 (4.5)
Mean	63	66
Daily Dose -- Mean (sd)	1.97 (0.13)	2.04 (0.15)
Median	2.00	2.00
Concurrent Boost Number (%)	13 (34%)	10 (34%)
Qualifying Oral Cavity Sites Mean (sd)	6 (3)	6 (3)
Median	5	5

The incidence of WHO grade ≥ 3 oral mucositis by 50 Gy in the Formulation 2 group was 29% lower than in the placebo group ($p = 0.041$; log-rank test) [Table D-8]. The relative reduction in WHO grade ≥ 3 oral mucositis on Formulation 2 at 50 Gy, compared with placebo, was 54%. Formulation 2 also reduced NCI clinical grade ≥ 3 oral mucositis with an absolute reduction in incidence of 46% at 50 Gy compared with placebo ($p = 0.005$; Log-rank test) and a relative reduction of 52%. The incidence of surgically placed PEG tubes for oral mucositis was also significantly lower on Formulation 2 compared with placebo (3% vs. 21%, $p = 0.037$; Fisher's exact test). [Table D-9] Opiate use was also lower in patients receiving Formulation 2 compared with placebo. The median total opiate score was 6 vs. 27, $p = 0.09$, and the median % of days on opiates during the study was 6% vs. 21%. ($p = 0.09$; Wilcoxon rank sum test)

Table D-8. Percentage of Patients Reaching Grade 3 or Greater on the WHO and NCI Scales

Cumulative dose of radiation in Gy	WHO Toxicity Scale		NCI Toxicity Scale	
	Formulation 2	Placebo	Formulation 2	Placebo
40 Gy	24%	46%	39%	67%
50 Gy	25%	54%	42%	88%
60 Gy	35%	54%	63%	92%

Table D-9. Incidence of Interventional PEG Tube Placement¹

	Placebo	Formula 2
	22%	3% ²

¹ Patients with pre-existing PEG tubes excluded.

² $p=0.037$; Fisher's exact test

The large reductions in the incidence of severe oral mucositis, WHO or NCI score greater than or equal to 3, in patients treated with Formula 2 relative to placebo is significant, and further confirms significant efficacy of NAC formulated with poloxamer 407 in a reverse-thermal gelling composition for use to treat oral mucositis resulting from cancer therapy. As previously discussed, patients with WHO or NCI grade 0, 1, or 2 oral mucositis were defined as

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successes and those with a grade ≥ 3 as failures. The reason for the dichotomization is due to the recognition that a score of 3 represents a highly morbid clinical event. Clinicians and regulatory agencies also recognize the importance of this dichotomization and the clinical impact to patients if they can be prevented from progressing to this point. The FDA has designated the Formula 2-type composition in oral mucositis as qualifying for Fast Track status because it is being investigated for the reduction of severe oral mucositis.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of this patent application or any patent issuing thereon.

Respectfully submitted,

Date: Sept 25th, 2006

By: Janice M. Troha
Janice M. Troha

Exhibit A
To Declaration of Janice M. Troha

Curriculum Vitae
Janice M. Troha

Professional Experience

Aug 2001-
Present **RxKinetix, Inc.**
 Boulder, Colorado

Vice President, Clinical Development and Regulatory Affairs
Treasurer, Secretary and Member of the Board of Directors (since 2004)

This position includes specific responsibilities for product development as well as considerable responsibility for general oversight of the company, including its strategic direction and operational performance. Key accomplishments include:

Conversion of the Company's business paradigm from a drug delivery focus to one that is focused on product development in the oncology care arena.

Redirection of the development strategy for the Company's lead product in oral mucositis and successful completion of Phase 2 development, thereby significantly increasing the valuation of the Company for shareholders.

Identification of product opportunities for the RxKinetix pipeline and creation of development strategies for such compounds to further enhance shareholder return.

Establishment and maintenance of relationships with experts to enhance visibility and development programs for RxKinetix products.

1994 - 1999 **Cortech, Inc.**
 Denver, Colorado

1998 - 1999 **Vice President, Product Development**

Responsible for the development of Cortech's technology portfolio, seeking collaborative/merger partners to further such development, and managing existing corporate collaborations and corporate communications. Key accomplishments in this position included:

Securement of a corporate partner for Cortech's lead neutrophil elastase inhibitor program.

Prevention of delisting from the Nasdaq through successful representation of the Company and its business to the Nasdaq listing panel.

Transition of the Company's business through an acquisition

1996 - 1998 Senior Director, Clinical Development and Regulatory Affairs
(reporting directly to the CEO)

Responsible for product and business development, regulatory affairs and corporate communications. Product development responsibilities included leadership of Cortech's stroke program (in preclinical development). Business development responsibilities included seeking collaborative partnerships for Cortech's protease inhibitor technology and the company's lead elastase and bradykinin antagonists. Communications responsibilities included preparation of press releases and sections of annual and quarterly reports that described Cortech's business. Regularly participated in shareholder meetings and conference calls regarding earnings. As a member of the management team, key accomplishments during this period were:

Modification of the company's business paradigm

Significant restructuring of operations and workforce.

1994 - 1996 Director, Clinical Development

Responsible for directing the clinical staff (approximately 17) in the clinical development of investigational compounds in the areas of traumatic brain injury, multiple trauma, cystic fibrosis, ARDS and sepsis. Accomplishments in this position included:

Successful conduct of one EOP2 meeting and two pre-IND meetings

Successful completion of Phase 2 clinical development for a product in acute traumatic brain injury. This resulted in a partnership with a large multinational pharma partner.

Preparation of an integrated safety summary that supported lifting the clinical hold on one of Cortech's compounds.

IND filing for the first human neutrophil elastase inhibitor to be studied in man, and initiation of clinical development.
(Phase Ib).

1984 - 1994 Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut

1993 - 1994 Associate Director, International Medical Operations

Responsible for overseeing the operations of the U.S. Medical Department and the integration and optimization of Medical Department processes and procedures worldwide. Reported directly to the U.S. Medical Director and participated in executive meetings. Key accomplishments included:

Re-engineering and consolidation of Medical Department structure and processes worldwide. The latter accomplished through appointment to an international team of 15 senior delegates led by the Boston Consulting Group.

Revision of all Medical Department job descriptions to create technical and managerial career tracks.

Preparation of international and national Medical Department SOPs.

1989 - 1993 Associate Director, Clinical Research

First non-MD in the company to achieve this position. Responsible for compound development from Phase I to Phase IV with five direct reports. Also responsible for the creation of an international training program on GCPs through leadership of the Company's International Training Committee. Specific accomplishments included the following:

International Medical Project Leader for an investigational compound in congestive heart failure. Successfully directed the program from IND filing through Phase III clinical development. Responsible for end-of-Phase II meeting with FDA. Designed and set up a large mortality trial.

Medical Project Leader for the development of a monoclonal antibody (Anti-ICAM) in cardiac transplantation and restenosis. Prepared medical sections of the IND and Phase Ib protocol in patients undergoing cardiac transplant.

Phase IV responsibility for antiarrhythmic and antihypertensive agents, including development and oversight of Phase IV trials and review of promotional materials.

Creation and conduct of a worldwide training program on Good Clinical Practices and clinical drug development for Medical Department personnel.

1987 - 1989 Manager, Clinical Research

Responsible for overseeing the implementation, conduct and reporting of clinical trials with two direct reports.

1984 - 1987 Medical Research Associate, Clinical Research

Assisted in the set up, monitoring, and analysis of Phase I-III trials and NDA preparation for an antiarrhythmic agent.

**1982 - 1984 Clinical Research Center, Tulane Medical Center,
 headed by Professor G. McMahon**

Study Coordinator

Responsible for the conduct of Phase II and III clinical trials in cardiovascular indications.

**1981 - 1982 St. Charles General Hospital
 New Orleans, Louisiana**

Staff Nurse on a unit which functioned as a step down from ICU.

Education

British education evaluated by the International Education Research Foundation (IERF) and rated as the equivalent of a Master's degree level in the USA.

**1984 State University of New York
 BS in Liberal Arts and Sciences**

**1980 Nightingale School of Westminster Hospital
 London, England
 Honors degree course in nursing - completed three years of course work for licensure.**

Areas of specialization included neonatal intensive care, open heart surgery and bone marrow transplantation.

**1976 University of Sheffield – Completed first year honors degree course in Pure Mathematics
 and Statistics then transferred to The Nightingale School.
 Member of the University Officers Training Corps.**

Publications

Katz S, Wahl J, Troha J, Sonnenblick E, and LeJemtel T. Specific Phosphodiesterase Inhibition and Maximal and Submaximal Exercise performance in Patients with Congestive Heart Failure. J. Cardiovasc Pharmacol 1989; 14 (Suppl 2): S45 - S48.

Katz S, Kubo S, Jessup M, Brozena S, Troha J, Wahl J, Cohn J, Sonnenblick E, and LeJemtel T. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Pimobendan, a New Cardiotonic and Vasodilator Agent, in Patients with Severe Congestive Heart Failure. AHJ 1992; 123:95-103.

Kubo S, Gollub S, Bourge R, Rahko P, Cobb F, Jessup M, Brozena S, Brodsky M, Kirlin P, Shanes J, Konstam M, Gradman A, Morledge J, Cinquegrani M, Singh S, LeJemtel T, Nicklas J, Troha J, and Cohn J. For the Pimobendan Multicenter Research Group. Beneficial Effects of Pimobendan on Exercise Tolerance and Quality of Life in Patients with Heart Failure: Results of a Multicenter Trial. Circulation 1992; 85:942-949.

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Narotam P.K., Rodell T.C., Troha J.M., Bhoola K.D., and van Dellen J.R. Traumatic Brain Contusions: A Clinical Role for the Kinin Antagonist CP-0127. *Acta Neurochirurgica* 1998; 140: 793 - 803.

Marmarou A, Nichols J, Burgess J, Newell D, Troha J, Burnham D, Pitts L and the American Brain Injury Consortium Study Group. Effects of the Bradykinin Antagonist Bradycor™ (Deltibant, CP-0127) in Severe Traumatic Brain Injury: Results of a Multicenter, Randomized, Placebo-controlled Trial. *J. Neurotrauma* 1999; 16: 431 -444

Abstracts

Chambers M.S., Welsh D.V., Scrimger R.A., Zhen W., Epstein J.B., Troha J.M., and Sonis S.T. RK-0202 for Radiation Induced Oral Mucositis. *Journal of Clinical Oncology*, 2006 ASCO Annual Meetings Proceedings Part I. Vol 24, No 18S, 2006: 5523.

Troha J.M., and Rodell, T.C. Experience with the experimental bradykinin antagonist Bradycor™ (CP-0127) in patients with the systemic inflammatory response syndrome (SIRS) and sepsis. Results of two clinical trials. Kinin '95 Fourteenth International Symposium on Kinins, September 10-15, 1995, Denver, CO. Immunopharmacology, 1996.

Shanley H.M., Kaufman L., Fletcher E.C., Westerman J., Matuschak G.M., Taylor Jr. R., Fein A.M., Levy H., Multz A., Rumbak M., Foulke G.E., Seneff M., Oakley R.D., Knaus W.A., Troha J.M., Sandhaus R.A., Rodell T.C.: CP-0127 (Bradycor™), a bradykinin antagonist, in SIRS and sepsis: results from the second multi-center trial using a seven-day infusion. *Chest*, 108:3, 1995.

Chambers M.S., Welsh D.V., Scrimger R.A., Zhen W, Epstein J.B., Sonis S.T.: RK-0202 for Radiation-Induced Oral Mucositis. *ASCO*, June 2006.

Industry- Related Documents

Authored the following documents:

Medical sections of three INDs and six Investigator Brochures, more than ten clinical trial protocols, six clinical trial reports, two integrated summaries of safety and one integrated summary of efficacy.

Invited Presentations

Results of a multi-center, randomized, placebo-controlled trial of CP-0127, a novel bradykinin antagonist, in patients with SIRS and sepsis. IBC's Fifth Annual Conference on Endotoxemia and Sepsis, June 19-21, 1995, Philadelphia, PA.

Troha J.M., and Rodell, T.C. Experience with the experimental bradykinin antagonist Bradycor™ (CP-0127) in patients with the systemic inflammatory response syndrome (SIRS) and sepsis. Results of two clinical trials. Kinin '95 Fourteenth International Symposium on Kinins, September 10-15, 1995, Denver, CO.

International Data. PERI's Annual Data Management Workshop 1993 to 1997.

CRAs and Data Managers - A Critical Link. PERI's Annual Data Management Workshop 1993 to 1997.

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Exhibit B
To Declaration of Janice M. Troha

Hamster Animal Study
Data From Blinded Photographic Oral Mucositis Scoring

Shown below are the individual oral mucositis scores that were assessed from photographs in a blinded fashion by two investigators in a hamster animal study (2 scores per animal per day of assessment, for a total of 12 – 14 scores per treatment group per day of assessment). Also shown are the means, standard deviation (SD), and standard error of the mean (SEM) of the scores. The initial N=7 hamsters per treatment group was decreased to N=6 in some groups due loss to anesthesia overdose or irradiation which occurred prior to mucositis assessment.

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	Animal	Days post-irradiation											
		6	8	10	12	14	16	18	20	22	24	26	28
Water Control	1	1	1	3	3	3	3	3	3	3	3	3	3
	2	1	1	2	4	5	3	4	4	4	4	3	3
	3	1	1	1	3	4	4	4	3	4	4	3	3
	4	1	1	1	4	4	4	4	4	4	4	3	4
	5	1	0	2	2	3	3	3	3	3	3	2	3
	6	1	1	1	2	3	3	4	3	3	3	3	3
	7	1	1	1	2	2	3	1	3	1	1	1	1
	8	1	1	1	2	2	3	1	2	1	2	1	2
	9	1	1	1	0	2	2	2	3	3	3	1	3
	10	1	1	1	1	2	3	3	3	3	3	3	3
	11	1	2	2	4	4	4	3	3	3	3	3	2
	12	1	1	2	4	4	4	3	3	3	3	3	3
Vehicle Control	1	0	0	1	2	2	3	3	3	3	3	1	2
	2	0	0	1	2	3	3	4	3	3	3	2	3
	3	0	1	2	2	3	2	2	2	1	1	1	2
	4	1	0	2	2	3	4	3	3	2	2	2	2
	5	1	0	2	2	3	4	3	3	3	3	3	2
	6	1	1	1	2	3	3	2	2	2	2	2	1
	7	1	1	2	2	3	3	3	3	3	2	3	1
	8	2	1	1	2	2	3	2	2	1	1	1	1
	9	2	1	1	2	2	3	2	2	2	1	1	1
	10	1	2	2	2	3	2	3	2	1	1	2	2
	11	1	1	1	3	3	2	3	3	2	2	2	2
	12	0	2	2	2	3	2	2	3	3	3	3	2
NAC in Water	1	1	1	1	2	2	2	1	1	2	2	2	2
	2	1	1	1	2	2	2	1	1	2	2	2	2
	3	1	1	1	3	2	2	1	0	2	1	1	2
	4	1	1	1	2	2	2	1	1	2	1	1	2
	5	1	3	2	2	2	2	1	1	2	1	2	2
	6	1	3	2	2	2	2	1	1	1	2	2	1
	7	1	1	1	2	2	0	2	2	2	3	3	1
	8	1	1	1	1	2	2	2	3	3	3	3	1
	9	2	1	1	1	2	2	2	1	2	1	1	1
	10	2	1	1	2	2	2	3	2	3	1	1	2
	11	1	1	1	3	2	2	3	3	3	3	3	2
	12	2	2	1	2	2	2	4	3	4	3	3	2
RK0282	1	1	1	1	2	2	2	1	1	1	1	1	2
	2	1	2	1	2	2	2	1	1	2	1	1	2
	3	0	1	1	1	2	2	2	1	2	1	1	1
	4	1	1	1	1	2	2	2	2	2	2	2	2
	5	1	1	1	1	2	2	1	1	2	1	1	1
	6	1	1	1	1	2	2	1	2	2	1	1	1
	7	1	2	2	1	2	2	1	3	2	1	1	1
	8	0	1	1	1	2	2	1	2	2	1	1	1
	9	1	1	1	1	2	2	2	2	1	1	1	1
	10	1	1	1	1	2	2	1	3	2	1	1	1
	11	1	1	1	2	3	2	1	2	2	1	2	1
	12	1	1	1	2	3	2	1	2	2	1	2	1
Summary	Mean	0.8	1.3	1.3	1.3	2.1	2.0	1.3	1.8	1.7	1.1	1.2	1.3
	SD	0.4	0.5	0.5	0.5	0.3	0.0	0.5	0.7	0.5	0.3	0.4	0.5
	SEM	0.1	0.1	0.1	0.1	0.1	0.0	0.1	0.2	0.1	0.1	0.1	0.1

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:)	Group Art Unit: 1614
ROSENTHAL et al.)	
Serial No.: 10/728,277)	Examiner: Roberts, Lezah
Filed: December 4, 2003)	<u>RULE 132 DECLARATION</u>
Conf. No.: 7142)	<u>OF ANTONY JAMES MATHEWS</u>
Atty. File No.: 42830-10010)	<u>(37 C.F.R. § 1.132)</u>
For: "TREATMENT OF MUCOSITIS")	
)	
)	

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir or Madam:

I, Antony James Mathews, residing at 2938 Kalmia Avenue #5, Boulder, CO 80301, USA, declare as follows:

I. Qualifications And Basis For Declaration:

I am currently employed by Endo Pharmaceuticals Colorado, Inc., formerly named RxKinetix, Inc., as Director, Formulation Development. I have significant experience working with poloxamer 407 and formulating compositions including poloxamer 407. The attached **Appendix A** is a detailed summary of my technical qualifications.

I have reviewed and considered an Office Action dated January 5, 2007 issued by the United States Patent and Trademark Office (the "Office Action") concerning the Pending Application, a copy of which is included in **Appendix B**.

I have reviewed and considered U.S. Patent Number 6,503,955 by Dobrozsi et al. ("Dobrozsi et al."), which was cited in the Office Action. A copy Dobrozsi et al. is included in **Appendix C**:

I have reviewed and considered the claims that are set forth in **Appendix D**.

I also have performed some tests on viscosity behavior on example compositions within the disclosure of Dobrozsi et al., and summaries of those tests are provided in **Appendix E**.

II. Excerpts Of Teachings Of Dobrozsi et al.

The following are some excerpts from Dobrozsi et al. These excerpts are each assigned reference numbers beginning with "D." In the discussion that follows in section III of this Declaration, I make reference as appropriate to various ones of these excerpts to identify portions of Dobrozsi et al. relevant to the discussion. Such References to these excerpts are made in brackets in the body of the discussion below using the assigned reference numbers.

D1. Column 2, lines 18-67.

Attempts to develop such compositions have been ongoing for a significant period of time. Examples of such compositions include intra-ocular dosage forms as disclosed in Edsman, K., Carlfors, J., Petersson, R., *Rheological Evaluation of Poloxamer as an In Situ Gel for Ophthalmic Use*, European Journal of Pharmaceutics Vol. 6 pp.105-112 (1998) herein incorporated by reference. Compositions such as these are broadly described as primarily aqueous solutions of block co-polymer surfactants, other wise referred to as "poloxamers", that are commonly known in the art. When formulated in water as somewhat concentrated solutions, or with water and co-solvents, the poloxamer solution remains as a pourable liquid. The most commonly reported example of this type of system consists of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water. These compositions are administered at room temperature as liquids. They form a gel upon reaching body temperature. The trigger for converting these compositions to a gel, therefore, is body heat.

In situ gelation of pharmaceutical compositions based on poloxamer that are biologically triggered are known in the art. For example Kim, C. K., Lee, S. W., Choi, H. G., Lee, M. K., Gao, Z. G., Kim, I. S., and Park, K. M.: *Trials of In Situ Gelling and Mucoadhesive Acetaminophen Liquid Suppository in Human*

Subjects, International Journal of Pharmaceutics vol. 174, pp. 201-207 (1998) incorporated herein by reference. Kim et al. discloses liquid suppositories for enhancing absorption of the pain and fever relieving drug acetaminophen.

U.S. Pat. No. 5,256,396, issued Oct. 26, 1993, to Colgate Palmolive Company, incorporated herein by reference, describes similar compositions containing poloxamer 407 and water at specified concentrations. Other products utilizing bio-triggers include those comprising poloxamer 407 at ranges preferably 12% to 17%. When combined with pharmaceutically active agents, these compositions are injected into the gingival space between the root of a tooth and the gum.

Poloxamers represent a large family of polymers that vary in molecular weight as well as in the percentage or portion of the block copolymer that is considered hydrophobic. Compositions comprising other poloxamers from this family having similar liquid/gelling characteristics are somewhat predictable, lacking only in the understanding of the required concentration of poloxamer. While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions. Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments.

D2. Column 3, lines 2-21.

The present invention covers pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments. The benefits of compositions formulated with such pourable liquid vehicles include retention of the compositions, materials and substances on the moistened surface. This in turn allow for effective delivery of a desired composition, material and substance in the vehicle that acts on targeted surface, resisting erosion or run-off even in an aqueous environment. Such pourable liquid vehicles have a number of utilities for delivery of all kinds of materials including but not limited to cleaning and treating surfaces of objects as well as biological or

living organisms, including living creatures.

Another object of this invention is to utilize such pourable liquid vehicles to deliver health care compositions and materials and substances to living creatures, particularly mammals, and most particularly humans. Even another object of the present invention is to develop a method for effective delivery of health care compositions, materials and substances.

D3. Column 3, lines 32-47.

The term "pourable liquid" as used herein means the physical state of the compositions of the present invention prior to formation of a gel.

The term "moistened surface" as used herein means any living or non-living surface having sufficient moisture in or on it to trigger rapid conversion of a pourable liquid to a gel.

The term "in situ gelation" as used herein means the conversion of a pourable liquid to a gel at a designated site or surface.

As used herein, the term "gel" describes the substance resulting from the combination of the pourable liquid and water, or bodily fluid containing mostly water. The gel is sufficiently viscous to remain at the site applied to, or ultimately targeted for, over a period of time sufficient for the compositions, materials and substances in the gel to bring about a desired result at the site they are delivered to.

D4. Column 3, line 65 through column 4, line 18.

The "viscosity" of a viscous material, also called viscosity index, is defined as the ratio of the shear stress applied into the material, divided by the rate of shear which results. Materials of a higher viscosity have a higher resistance to flow, or to forces which can induce flow, than a lower viscosity material. All viscosities listed herein are at a shear rate of about 50 per second unless otherwise indicated. All of the rheologic characteristics given herein can be measured in a

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controlled rate or a controlled stress rotational viscometer capable of some operation in a controlled rate mode, for Example Haake RS 150 by Haake GmbH, Karlsruhe, Germany; Carrimed CSL 500 Controlled Stress Rheometer by TA Instruments, New Castle, Delaware; and Rheometric SR5, by Rheometric Scientific, Piscataway, N.J.

Specifically, when subject to constant shearing rate of about 50 per second at normal ambient temperature (approx. 25° C.), the present liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds.

D5. Column 4, lines 19-32.

The value of a composition's triggered viscosity ratio ("T") is useful in determining the degree to which a composition exhibits the above described gelling characteristic. The formula and procedure for determining the triggered viscosity ratio is set forth below.

It is desirable for the compositions of the present invention to exhibit a triggered viscosity ratio of at least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10 wherein the triggered viscosity is defined by the following formula or ratio:

$$T = \eta_g / \eta_l$$

where η_g = viscosity of the gel and

where η_l = viscosity of the pourable liquid

D6. Column 4, lines 33-48.

The pourable liquid vehicle of the present invention must be selected and formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture. Examples of these fluids are saliva, gastric fluid, intestinal fluid, extracellular fluid present under the

skin at the site of a subcutaneous injection, or in muscle tissue at the site of an intramuscular injection, cerebrospinal fluid, vaginal fluid, fluid exudate from an open wound or ulcer, tear fluid, rectal fluid, or any other bodily fluid of an animal which contains in large measure water. In other words, after the pourable liquid vehicle contacts with the bodily fluid, the viscosity of the pourable liquid vehicle becomes greater than the viscosity of either the pourable liquid vehicle itself prior to mixing, or the bodily fluid alone.

D7. Column 4, line 33 through column 5, line 33.

The triggered viscosity ratio of a pourable liquid vehicle can be determined by one skilled in the art using appropriate viscosity measuring instruments, and is exemplified by the following method. First, the viscosity of the pourable liquid vehicle (η_r) is determined in a rheometer using a shear rate of 50 per second at 25° C. For the determination of η_r , 1 ml of the pourable liquid vehicle is placed onto the plate of a Haake RS 150 rheometer. The temperature is controlled in the range of typical room temperature, about 25° C. A cover is used on the measuring system and a solvent-saturated atmosphere provided to prevent evaporation of water, ethanol, or other volatile components from the sample during the test. A 35 mm diameter parallel plate measuring system is lowered onto the sample, leaving a gap of about 1 millimeter, and an equilibration shearing of approximately 10 per second is applied for 10 seconds. Then, a constant shearing rate of 50 per second is applied for 30 seconds. The viscosity η_r is read from the instrument at the 30 second time point.

For the determination of η_g , two dilutions of the pourable liquid vehicle are made with water. The first dilution is made to contain 75% by weight of the pourable liquid vehicle, and 25% by weight of additional water. The second dilution is made to contain 50% by weight of pourable liquid vehicle and 50% by weight of additional water. The pourable liquid vehicle and water are combined in a vial and a tight seal applied to prevent evaporation of components. The vial contents are mixed in an unusual manner, by repeated centrifugation. This is

necessary since some of the combinations are very viscous gels. Specifically, the vials are centrifuged (using for example a Beckman GS-6R centrifuge, available from Beckman Instruments, Palo Alto, Calif.) 20 minutes at 3000 RPM and 25° C. for at least four separate centrifuge runs. After each run the vials are inverted. Additional runs are conducted in the centrifuge to ensure complete mixing. 1 ml of the gelled sample is then loaded onto the plate of the same rheometer used for the measurement of η_f , except that the temperature is controlled at the normal body temperature of a human, 37° C. An identical rheometer measurement program is used as for determination of η_f . The triggered viscosity factor for both the 25% and 50% dilution of the sample is calculated from η_f and η_g as described by the formula above. These two dilutions have been found to be useful for measuring the gelling functionality of the pourable liquid vehicles of the invention in a standardize method, because some of the pourable liquid vehicles may require a greater or lesser amount of water in order to trigger the gelling character. The use of other water dilutions for determination of η_g , ranging from about 5% up to about 70%, would also be expected to provide a demonstration of the unique, gelling character of the invention, but the dilution which yields a maximal value of T varies depending upon the exact pourable liquid vehicle being tested.

D8. Column 5, lines 34-47.

All percentages of the components comprising the invention are herein referred to their weight in the pourable liquid vehicle as a whole.

The present invention is a pourable liquid vehicle comprising:

- (a) from about 26% to about 100% polyoxyalkylene block copolymer;
- (b) from about 0% to about 70% glycol; and
- (c) from about 0% to about 50% water;

wherein said vehicle is used to deliver compositions, materials and substances to moistened surfaces and aqueous environments said vehicle has a viscosity value

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η_r less than or equal to 7 pascal-seconds and the value T greater than or equal to about 1.3.

D9. Column 5, lines 51-54.

Polyoxyalkylene block copolymers herein referred to as "poloxamers" are nonionic block copolymers of ethylene oxide and propylene oxide corresponding to the following structure:

D10. Column 6, lines 61-63.

Preferred glycols are selected from the group consisting of ethanol, glycerol and propylene glycol, and mixtures thereof.

D11. Column 6, line 66 through column 7, line 4.

In addition to the poloxamers, and, or the glycol, it is desirable in some of the pourable liquid vehicles of the present invention to include water. Water is useful at a level from 0% to about 50%, preferably about 1% to about 46%, most preferably from about 2% to about 41% of the pourable liquid vehicle.

D12. Column 7, lines 7-25.

Preferred embodiments of the present invention utilizing the combination of poloxamers, polyols and water include the following:

1. from about 26% to about 65% Pluronic F127, from about 22% to about 38% ethanol and from about 8% to about 45% water.
2. from about 52% to about 60% Pluronic F108, from about 20% to about 25% ethanol and from about 17% to about 27% water.
3. from about 25% to about 50% Pluronic P105, from about 45% to about 65% propylene glycol and from about 5% to about 20% water.

4. from about 37% to about 77% Pluronic P105, from about 12% to about 28% ethanol, and from about 10% to about 45% water
5. from about 26% to about 49% Pluronic F127, from about 2% to about 12% ethanol, from about 30% to about 68% propylene glycol, and from about about [sic] 7% to about 40% water.

III. The Teachings Of Dobrozsi et al. In Relation To Claims In Appendix D.

Claim 1, as set out in Appendix D, identifies a composition useful for treatment of oral mucositis. According to Claim 1, the composition must include at least the three identified components in a particular formulation, namely: N-acetylcysteine, poloxamer 407 in an amount of 5 to 20 weight percent of the composition, and carrier liquid comprising water in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart reverse-thermal viscosity behavior. Also, the composition exhibits reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C, and when at some reduced temperature in the range of 2°C to 8°C the composition is an aqueous solution with both the poloxamer 407 and the N-acetylcysteine dissolved in the water.

Reverse-thermal viscosity is a property that is not common in liquid materials. The common effect of changes in temperature on the viscosity of liquids (including most liquid solutions) is that the viscosity of the liquid decreases with increasing temperature. Some aqueous solutions of poloxamer 407, however, are anomalous because at some temperatures the solutions exhibit a viscosity increase with increasing temperature. This uncommon type of viscosity behavior is known as "reverse-thermal", because the relationship between temperature and viscosity is a reverse of that which is most common for liquid formulations. Some, but not all, aqueous solutions of poloxamer 407 exhibit reverse-thermal viscosity behavior at some temperatures between 1°C and 37°. Some factors affecting whether a particular aqueous solution of poloxamer 407 would exhibit reverse-thermal viscosity behavior include the concentration of poloxamer 407 and the nature and concentrations of other components in the solution. Determining whether any particular aqueous solution of poloxamer 407 exhibits reverse-thermal viscosity behavior within any particular temperature range is a simple matter of making the

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solution and testing the viscosity of the solution at various temperatures within that range, which is well within the capabilities of an ordinarily skilled chemist.

Dobrozsi et al. disclose what they call a "pourable liquid vehicle", which they disclose as being useful for delivering materials to moistened surfaces and aqueous environments, where the delivered materials are retained at the moistened surface [D2]. Dobrozsi et al. provide an extensive listing (at column 7, line 26 through column 9, line 27) of possible materials that might be delivered using the pourable liquid vehicle.

Dobrozsi et al. disclose that a property of their pourable liquid vehicle is that it forms a gel when it combines with water or bodily fluid containing mostly water, and that the gel that forms is sufficiently viscous to remain at the site of application, to retain the delivered material at that site [D2, D3, D6]. It is the contacting and mixing of the pourable liquid with water or such bodily fluid that causes, or triggers, the conversion of the pourable liquid vehicle to the gel form [D6].

The pourable liquid vehicle of Dobrozsi et al. has a viscosity of less than 7 pascal seconds, and more preferably smaller than 1 pascal second [D4, D8]. A viscosity of 7 pascal seconds is equal to 7000 centipoises (cP). The viscosity of the gel formed from the pourable liquid vehicle has a viscosity at least 1.3 times, and most preferably 10 times, as large as the viscosity of the pourable liquid vehicle [D5]. Dobrozsi et al. refer to the ratio of the viscosity of gel to the viscosity of the pourable liquid vehicle as the "triggered viscosity ratio" [D5]. The triggered viscosity ratio is dependent upon the degree of dilution to which the pourable liquid is subjected, and Dobrozsi et al. describe determination of this triggered viscosity ratio for any given degree of dilution by measuring the viscosity of that pourable liquid vehicle at 25°C (typical room temperature), diluting the pourable liquid vehicle with water by the desired amount to form a gel (Dobrozsi et al. suggest doing dilutions at 25:75 and 50:50 parts water to parts pourable liquid vehicle), measuring the viscosity of the resulting gel at 37°C (human body temperature), and dividing the measured viscosity of the gel by the measured viscosity of the pourable liquid vehicle [D7].

On page 4 of the Office Action, the patent Examiner asserts that the viscosity of the pourable liquid vehicle of Dobrozsi et al. was shown to increase with an increase in temperature from room temperature to 37°C. The Examiner's exact statement is quoted as follows:

The pourable liquid vehicle of the disclosed invention [of Dobrozsi et al.] were formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture (col. 4, lines 33-48). The viscosities of the formulated vehicles were measured at room temperature and 37°C the temperature inside the human body. It was disclosed the viscosity of the compositions increased at the higher temperature, therefore encompassing claim 1. [Emphasis as in original.]

The Examiner's reference to the higher viscosity at 37°C relative to the viscosity at room temperature must relate to that portion of Dobrozsi et al. describing the determination of the triggered viscosity ratio, which, as discussed above, involves measurement of the viscosity at 25°C of the pourable liquid and measurement of the viscosity at 37°C of the gel that forms after dilution of the pourable liquid vehicle. This portion of Dobrozsi et al. is quoted in excerpt D7 above. However, that portion of Dobrozsi et al. does not describe a reverse-thermal viscosity behavior for the pourable liquid vehicle of Dobrozsi et al. As discussed above, Dobrozsi et al. describe the conversion of the pourable liquid vehicle to a gel as being caused by dilution of the pourable liquid with water or certain bodily fluids, not by temperature change. It seems apparent that the reason Dobrozsi et al. measure the temperature of the gel at 37°C is simply because that is the temperature to which a composition would be subjected in a human body following administration. Regardless that Dobrozsi et al. measure the viscosity of the pourable liquid vehicle and the gel at different temperatures, the disclosure of Dobrozsi et al. is that formation of the gel is caused by dilution. Formation of a gel caused by dilution of the pourable liquid vehicle as disclosed by Dobrozsi et al. is not reverse-thermal viscosity behavior.

Moreover, reverse-thermal viscosity behavior is a property of a material exhibited when the material is subjected to change in temperature, all other variables remaining constant. As a property of a material, reverse-thermal viscosity behavior does not involve a compositional change to the material. The conversion of the pourable liquid vehicle to a gel as disclosed by Dobrozsi et al., however, is based not on a temperature effect on viscosity, but upon a compositional change that occurs when the pourable liquid vehicle is diluted with water or certain bodily fluids. The gel described by Dobrozsi et al. is a different composition than the pourable liquid vehicle, due to the addition of the dilution liquid. Comparing the viscosity of the

gel at one temperature to the viscosity of the pourable liquid vehicle at a different temperature provides no information about the effect of temperature on the viscosity of either the gel or the pourable liquid, because they are different compositions. Claim 1, as set forth in Appendix D, describes a composition having a property of reverse-thermal viscosity behavior (i.e., that the viscosity of the composition increases with increasing temperature of the composition). Reverse-thermal viscosity behavior is significantly different than what Dobrozsi et al. describe, which is a change of composition through dilution of the pourable liquid vehicle to form a new composition (containing the dilution liquid) that is in the form of a gel. The conversion of the pourable liquid to a gel with a change in composition is not reverse-thermal viscosity behavior.

Dobrozsi et al. make reference to reverse-thermal viscosity behavior only in the background section of that document, with the reference being to certain compositions made using poloxamers [D1]. Concerning those background compositions, Dobrozsi et al. recognize that they have a reverse-thermal gelation property, stating:

These compositions are administered at room temperature. They form a gel upon reaching body temperature. The trigger for converting these compositions to a gel, therefore, is body heat. [D1, emphasis added.]

Dobrozsi et al. then assert that these previously known poloxamer compositions are inadequate, and state:

While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions. Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments. [D1, emphasis added.]

As discussed above, Dobrozsi et al. disclose that formation of a gel from their pourable liquid vehicle is triggered not by heat, but by a compositional change, i.e., dilution with water or certain bodily fluids. It is clear that Dobrozsi et al. are not relying on reverse-thermal viscosity behavior as a mechanism for gel formation, and Dobrozsi et al. are proposing their pourable liquid vehicle as a superior alternative to those previously known compositions that rely on

reverse-thermal viscosity behavior for gel formation. Gel formation through viscosity increase caused through compositional change by the addition of a triggering component, e.g., aqueous dilution fluid added to the pourable liquid vehicle in Dobrozsi et al., involves a fundamentally different mechanism for viscosity increase than the mechanism of reverse-thermal viscosity increase, which is caused simply by an increase in temperature. Making a drug delivery formulation including reverse-thermal viscosity behavior would not be obvious from the teaching of Dobrozsi et al., which finds such formulations as inadequate and offers an alternative to address such inadequacy.

It is true that Dobrozsi et al. disclose that one of the components of their pourable liquid vehicle is a poloxamer, which Dobrozsi et al. refer to as "polyoxyalkylene block copolymers" [D9]. But it is clear that Dobrozsi et al. are not using the poloxamer for its ability to be formulated to make compositions exhibiting reverse-thermal viscosity behavior and, as discussed above, not all poloxamer formulations exhibit such reverse-thermal viscosity behavior.

Dobrozsi et al. require that their pourable liquid vehicle contains 26 weight percent to 100 weight percent polyoxyalkylene block copolymer, and optionally up to 70 weight percent glycol and up to 50 weight percent water [D8]. Moreover, Dobrozsi et al. require that within these compositional constraints, the pourable liquid vehicle must also be formulated so that contacting and mixing the pourable liquid vehicle with a body fluid containing mostly water causes the formation of a gel [D3, D6]. Dobrozsi et al. list as preferred embodiments for the pourable liquid vehicle certain compositions including "Pluronic F127" [D12], which is a poloxamer 407, the type of polymer specified in Claim 1 as set forth in Appendix D. These preferred compositions include at least 26 weight percent Pluronic F127 and either ethanol and water in certain concentrations or ethanol, propylene glycol and water in certain other concentrations [D12].

Based on a consideration of the teachings of Dobrozsi et al. and my experience with formulations including poloxamer 407, e.g., Pluronic F127, I expected that many, if not most, of the pourable liquid vehicle compositions described by Dobrozsi et al. would not exhibit reverse-thermal viscosity behavior of the type as recited in Claim 1 of Appendix D. Many of the possible compositions for pourable liquid vehicle within the teachings of Dobrozsi et al. contain 100% poloxamer, while others contain only poloxamer and a glycol, and none of the possible compositions for the pourable liquid vehicle contain more than 50% water.

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To test my expectation, I prepared some example compositions that would be within the teachings of Dobrozsi et al. for the pourable liquid vehicle to test their viscosity behavior. Table 1 below summarizes four different test compositions that I prepared for testing, all including poloxamer 407. A summary of the preparation and viscosity testing of each of these example compositions is included in Appendix E.

TABLE 1

Example No.	Poloxamer 407 weight %	Water weight %	Ethanol weight %	Propylene Glycol Weight %	Viscosity Behavior
1	26	50	24	--	No reverse-thermal viscosity behavior
2	26	50	--	24	Reverse-thermal viscosity behavior, but extremely high viscosity unsuitable as pourable liquid vehicle of Dobrozsi et al., which must have viscosity of less than 7000 Cp
3	26	37.1	36.9	--	No reverse-thermal viscosity behavior
4	26	37.1	--	36.9	Could not successfully prepare a homogenous mixture for testing

For all example compositions, poloxamer 407 was used at a concentration of 26 weight percent, because that is the minimum concentration of poloxamer 407 permitted by Dobrozsi et al. [D8, D12] and is closest to the range of poloxamer 407 concentrations required in Claim 1 of Appendix D (5 to 20 weight percent). All tests included water in an amount so that in all example compositions water is the largest liquid component, so that all example compositions would be aqueous solutions, because an aqueous solution is a requirement of Claim 1 of Appendix D. Two example compositions (Examples 1 and 2) used 50 weight percent water, because that is the maximum water concentration permitted by Dobrozsi et al. [D8, D11]. Two other example compositions (Examples 3 and 4) used 37.1% water, as a minimum amount of water that could be used in combination with another liquid component to make a solution that would be aqueous. The remaining portion of each example composition was then made up of

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either ethanol (Examples 1 and 3) or propylene glycol (Examples 2 and 4). Ethanol was used because it is specified by Dobrozsi et al. for use in preferred compositions made using poloxamer 407 [D12] and it is used extensively with poloxamer 407 (Pluronic F127) in the specific technical examples disclosed by Dobrozsi et al. in columns 9-17. Propylene glycol was used because it is listed by Dobrozsi et al. as a preferred glycol for use to make the pourable liquid vehicle [D10], and because it was used extensively in the technical examples presented by Dobrozsi et al. in columns 9-17.

Except for Example 4, after preparation, each of the example compositions were tested for viscosity behavior over a temperature range of 0°C to 40°C, which covers the 1°C to 37°C range of Claim 1 in Appendix D. I was unable after significant effort to obtain a homogeneous mixture of Example 4 suitable for viscosity testing, and that example composition was not tested for viscosity behavior. A brief summary of the results of the viscosity testing is presented in Table 1. A more extensive discussion of the test procedures and results for each of the examples is presented in Appendix E.

In summary, neither of the example compositions containing ethanol (Examples 1 and 3) exhibited reverse-thermal viscosity over any range of temperatures between 0°C and 40°C. (See, Figures 1 and 3, respectively, in Appendix E.) The compositions of those examples exhibited the normal viscosity behavior of steadily decreasing viscosity with increasing temperature. The composition of Example 2, containing 50% water and 24% propylene glycol did exhibit reverse-thermal viscosity behavior. (See, Figure 2 in Appendix E.) It is noted, however, that the viscosity of the composition of Example 3 at all temperatures tested was over a million cP, or over two orders of magnitude higher than the maximum viscosity of 7000 cP specified by Dobrozsi et al. for their pourable liquid vehicle, and likewise the composition of Example 2 is not a flowable medium at a refrigerated temperature in a range of from 1°C to 10°C as required in Claim 142 of Appendix D and is not suitable for use as a mouthwash as required in Claim 149 of Appendix D.

The testing confirmed my expectation that at least many of the pourable liquid vehicle compositions proposed by Dobrozsi et al. would not exhibit reverse-thermal viscosity behavior. This is not surprising, because, as discussed above, the pourable liquid vehicles of Dobrozsi et al. were prepared to address problems identified by Dobrozsi et al. with prior compositions that exhibited reverse-thermal viscosity behavior, and Dobrozsi et al. teach away from using reverse-

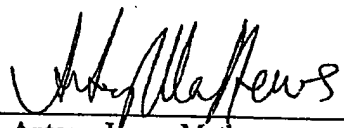
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thermal viscosity behavior as a mechanism for drug delivery, finding that mechanism to be inadequate, as discussed above.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of this patent application or any patent issuing thereon.

Respectfully submitted,

Date: 7-3-2007

By: 
Antony James Mathews

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APPENDIX A
TO
DECLARATION
OF
Antony James Mathews

Detailed Summary Of Technical Qualifications

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Curriculum Vitae: Dr. Antony James Mathews

Date : May 30, 2007

Nationality : New Zealand

Home Address : 2938 Kalmia Avenue #5, Boulder, CO 80301, USA

Degrees Held : BSc, PhD

Biotechnology Experience

- Director of Formulation Development. Member of CMC team. Leading several direct reports in support of all formulation characterization and stability issues for drug manufacturing and scale up.
- Key member of manufacturing and process development troubleshooting teams. Project leader for a 15 member multidisciplinary team including engineers, scientists and management, reporting directly to senior management and which solved critical protein purification problems saving \$200,000 US per month.
- Project leader for the development of platelet and reagent red cell preservation media. Achieved comprehensive resolution of the platelet project in nine months. Appointed to Deputy Director of Health Sciences in recognition of experience and mentoring of colleagues.
- Expert in protein purification from milligram to multi-gram scales for the support of research, pre-clinical studies, purification process development and troubleshooting. Extensive expertise in protein chemistry including protein folding, chemical modification and crosslinking, and detailed chemical analysis of proteins.
- Experienced in the development of biochemical assays based on chromatography, UV-visible spectroscopy, mass spectrometry and chemical kinetics, and used to support research, product development and manufacturing.
- Expert in biophysical chemistry techniques used in structure-function screening, particularly in the reaction kinetics and equilibrium measurements of protein-small molecule interactions and protein-protein interactions.
- Trained and managed biology, protein purification, and biophysical chemistry research groups ranging in size from a few research associates to large groups including several PhD scientists.

Research and Development Experience

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October 2006 – Present: Director, Formulation Development, Endo Pharmaceuticals
Colorado, Boulder, Colorado, USA

RxKinetix was acquired by Endo Pharmaceuticals of Chadds Ford, Pennsylvania in mid-October. My position and duties remain unchanged.

January 2006 – October 2006: Director, Formulation Development, RxKinetix Inc., Boulder, Colorado, USA.

Responsible for formulation development and analysis of pharmaceuticals, including assay development, biophysical measurements, and stability measurements.

October 2005 – December 2005: Postdoctoral research in the laboratory of Professor Tom Brittain, School of Biological Sciences, University of Auckland, Auckland, New Zealand. In collaboration with Associate Professor Angela Fago, a visiting researcher from the University of Aarhus in Denmark, performed biochemical and biophysical investigations of ligand binding and electron transfer reactions of recombinant neuroglobin and cytochrome *c*. This work was undertaken while waiting for my USA O-1 visa prior to taking my position at RxKinetix.

May 2003 – September 2005: Director of Research and Development, ICPbio Limited, Auckland, New Zealand.

Directed the activities of a small R&D group in support of company goals, including bioprocess and protein purification development of regulated protein products and assay development. Provided support for internal customers and external research interactions, including supervision of an MPhil. student, co-authoring a successful multiple institution grant application to investigate automated milk protein fractionation, and establishing contract research for embryo storage products.

July 2002 - February 2003: Head of Biochemistry, Genesis Research and Development Corporation Limited, Auckland, New Zealand.

Managed research groups and troubleshooting for the identification of proteins and peptides in plant phloem sap using two dimensional electrophoresis, two dimensional HPLC, and mass spectrometry.

July 2001 - June 2002: Project Leader - BioStore, Genesis Research and Development Corporation Limited, Auckland, New Zealand.

Assembled and managed research group characterizing blood platelet storage solutions and storage solutions with improved preservation of the antigen profiles of reagent red blood cells. Identified key research approaches, arranged and managed external research contracts.

March 2000 - June 2001: Senior Research Scientist, working for Professor John S. Olson, Department of Biochemistry and Cell Biology, Rice University, Houston, Texas. Simplified synthesis of mixed metal hybrid hemoglobins. Measurements of apo-hemoglobin stability. Hemoglobin-NO chemistry.

April 1999 - February 2000: Research Fellow, working for Associate Professor Tom Brittain, School of Biological Sciences, University of Auckland, Auckland, New Zealand.

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Protein purification and analysis for X-ray crystallography and NMR experiments. Mechanism of heme insertion during hemoglobin biosynthesis. Isolation of peripheral blood reticulocytes by isopycnic density gradient ultracentrifugation. NMR studies of heme disorder in adult and recombinant human embryonic hemoglobins. Purification and analysis of recombinant hemoglobins from yeast by ion exchange and size exclusion chromatography, chromatofocusing, and reversed phase HPLC.

September 1990 - August 1998: Research Scientist II and III at Somatogen, Inc., Boulder, Colorado (known as Baxter Hemoglobin Therapeutics since June 1998).

Key member of protein purification process development and troubleshooting teams. Assay development using numerous biophysical/biochemical techniques. Developed laboratory facilities. Trained and managed research groups studying protein biophysical chemistry and protein purification from milligram to tens of grams scale. Biophysical and chemical analysis of self-associating proteins. Structure-function screening of recombinant hemoglobins for product development. Protein engineering of hemoglobin to decrease reactivity towards nitric oxide. Site directed chemical crosslinking of hemoglobin.

December 1986 - July 1990: Postdoctoral Research Fellow, working for Professor John S. Olson, Department of Biochemistry and Cell Biology, Rice University, Houston, Texas. Heme pocket structure-function relationships in recombinant human hemoglobins. Laser flash photolysis and stopped-flow rapid kinetics of ligand binding to hemoglobin and myoglobin. Isolation of inclusion bodies, protein purification and refolding.

February - November 1986: Postdoctoral Research, working for Professor Barry T. Nall, Department of Biochemistry and Molecular Biology, Medical School, University of Texas Health Science Center at Houston (now at UTHSC San Antonio). Thermodynamic stabilities and folding kinetics of yeast cytochrome *c*. Denaturant and thermally induced unfolding of proteins.

University Education

BSc (1981, Chemistry and Biochemistry) and PhD (1986, Biochemistry) degrees were awarded by the University of Auckland, New Zealand.

Doctoral Research Topic : Chemically Modified Cytochromes *c*.

Doctoral Advisor : Associate Professor Tom Brittain.

Scholarships : New Zealand Universities Postgraduate Scholarship.

Publications

The reaction of Neuroglobin with Potential Redox Protein Partners Cytochrome *b₅* and Cytochrome *c*.

A. Fago, A.J. Mathews, L. Moens, S. Dewilde, and T. Brittain. *FEBS Letters*, (2006), 580, 4884-4888.

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Genetically Fused Globin-like Polypeptides having Hemoglobin-like Activity
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Hemoglobin-like Protein Comprising Genetically Fused Globin-like Polypeptides
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D.C. Anderson, A.J. Mathews and G.L. Stetler
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App. Serial No. 10/788,277

APPENDIX B
TO
DECLARATION
OF
ANTONY JAMES MATHEWS

Copy of Office Action Dated January 5, 1007



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,277	12/04/2003	Gary I. Rosenthal	42830-10010	7142
25231 7590 01/05/2007 MARSH, FISCHMANN & BREYFOGLE LLP 3151 SOUTH VAUGHN WAY SUITE 411 AURORA, CO 80014			EXAMINER ROBERTS, LEZAH	
			ART UNIT 1614	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE 3 MONTHS		MAIL DATE 01/05/2007	DELIVERY MODE PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/728 277

Examiner

Lezah V. Roberts

Applicant(s)

ROSENTHAL ET AL.

Art Unit

1814

— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136. In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *E. parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 15, 17, 19, 20, 22, 24, 25, 31, 35, 38, 133-137 and 142-148 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 15, 17, 19-20, 22, 24-25, 31, 35, 38, 133-137 and 142-148 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date A-B
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

This office action is in response to the amendment filed September 29, 2006. All previous rejections have been withdrawn unless stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action mailed March 23, 2006.

Response to Declaration Under 37 CFR 1.132

The Declaration of Janice M. Troha under 37 CFR 1.132 filed September 29, 2006 is insufficient to overcome the rejection of the instant claims based upon 35 USC 102 and 103 as set forth in the last Office action because the Declaration shows methods of using the compositions. The claims are directed to a composition, however not a method of use. The intended use of a composition carries no weight in determining patentability because the compositions suggested by the references are substantially the same as the compositions of the instant claims.

Claims

Claim Rejections - 35 USC § 103 (Previous Rejection)

Claims 15, 22-23 and 136-141 were rejected under 35 U.S.C. 103(a) as being unpatentable over Krezanoski (US 4,188,373) in view of Boggs (US 5,358,705). The rejection is maintained in regards to claims 15, 22, 136-137 and 140.

Applicant argues Krezanoski does not disclose N-acetylcysteine (NAC), for any purpose. Applicant further argues based on the Troha Declaration, the disclosure of Boggs et al. would not lead to an expectation that NAC would be efficacious for treatment of mucositis occurring as a side effect of cancer therapy, the pathogenesis of which does not appear to be due to the presence of bacteria.

In response to applicant's argument that Krezanoski does not disclose NAC for any purpose and the disclosure of Boggs et al. would not lead to an expectation that NAC would be efficacious for treatment of mucositis occurring as a side effect of cancer therapy, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Claim Rejections - 35 USC § 103 – Obviousness (New Rejection)

Claims 1, 15, 19, 31, 35, 38, 133-137, 142-143 and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955).

Dobrozsi et al. disclose pourable liquid vehicles comprising an aqueous or nonaqueous polymer solution. The vehicles comprise a polyoxyalkylene block copolymer, water and glycols. The copolymer comprises polyoxypropylene and polyoxyethylene and makes up 25% to 77% by weight of the vehicle. Water makes up

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5% to 45% of the composition (col. 7, lines 5-25). The glycols used, such as polyethylene glycol, which encompasses claim 11, make up 0 to 70% (col. 6, lines 50-53). Pluronic F-127 is a preferable block copolymer used in the compositions. The pourable liquid vehicle of the disclosed invention were formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture (col. 4, lines 33-48). The viscosities of the formulated vehicles were measured at room temperature and 37°C the temperature inside the human body. It was disclosed the viscosity of the compositions increased at the higher temperature, therefore encompassing claim 1. The disclosed liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds (col. 5, lines 12-17), which encompasses no larger than 60cP of the instant claims. The desired value of a composition's triggered viscosity ratio is least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10. The triggered viscosity is defined as the viscosity of the gel divided by the viscosity of the liquid. Using this calculation the gel viscosity is greater than 80cP, which encompasses the instant claims. The pourable liquid vehicles have a number of utilities including delivery of therapeutic agents. These include agents selected from the group consisting of expectorants/mucolytics, antioxidants and mixtures thereof (col. 7 lines 48-51). Expectorants/mucolytics include N-acetylcysteine. The active agents are added to the vehicles ranging up to 5% weight of the total composition according to the disclosed examples, which encompasses claim

Art Unit: 1614

15. The reference discloses several different dosage forms including gels, rinses, sprays and liquid filled capsules for intra-oral administration. Flavors and preservatives are also used in the disclosed compositions (see examples), as recited in claims 35 and 38.

The reference differs from the instant claims insofar as it does not disclose specifically using N-acetylcysteine in a composition comprising poloxamers 407. The reference is not anticipatory insofar as one must "pick and choose" from different lists of active agents and poloxamers. That being said, it would have been obvious in a self-evident manner to have selected N-acetylcysteine from one list and poloxamers 407 from another, motivated by the unambiguous disclosure of each individually, and consistent with the basic principle of patent prosecution that a reference should be considered as expansively as is reasonable in determining the full scope of the contents within its four corners.

2) Claims 17, 20, 24-25 and 137, 140, 144-145 and 147-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955) in view of Stratton et al. (US 5,861,174).

The primary reference is discussed in subsection 1, above. The reference differs from the instant claims insofar as it does not disclose the compositions comprise 0.1 to 20% of the preferred block copolymer, the compositions comprise about 10% or N-acetylcysteine and the composition were made when the liquid carrier was 5°C.

Stratton et al. disclose pharmaceutical compositions for the delivery of pharmacologically active proteins. The polypeptides make up 0.5% or greater of the disclosed compositions (col. 3, lines 38-45). In one embodiment of the invention, the polypeptide comprises 0.5 to 50% by weight of the compositions (col. 6, lines 46-50). The polymers of disclosed invention provide a sustained release delivery system for active agents or drugs (col. 1, lines 51-53). The delivery vehicle comprises block copolymers, polyoxyethylene-polyoxypropylene namely Pluronic polyols, or poloxamers. Poloxamers have the ability to gel as a function of temperature and polymer concentration. Poloxamers having molecular weights below 10,000, do not form gels at any concentration, therefore Pluronic F-127 and Poloxamer 407 are the polymers of choice for the disclosed invention (col. 2, lines 18-60). These polymers have the characteristics of being liquid at temperatures below room temperature but will form a gel as they are warmed (col. 4, lines 38-41). The aqueous polymer solutions may be formed in two ways, by a cold process or by a hot process. The cold process involves dissolving the polymer at a temperature from about 5°C to 10°C (col. 5, lines 20-34). When adding the polypeptide, it is preferred to add the agent at a temperature of about 0°C to 10°C. These conditions encompass claims 24-25. Raising the sample temperature above the gel point of the poloxamer results in an even distribution of protein particles throughout the polymer gel (col. 6, lines 1-7). The copolymer will not form a gel at a concentration outside the range of about 20% to 30% by weight (which overlaps the concentration of the instant claims), but it was discovered other compounds could be added to the compositions in order for the copolymer to form a gel

at concentrations lower than 20% by weight, which encompasses claim 137 as well as claim 20.

The reference differs from the instant claims insofar as it does not disclose compositions comprising glutathione or its precursors and the viscosities of the compositions before and after the temperature change.

It would have been obvious to adjust the amount of poloxamer in the compositions of the primary reference motivated by the desire to obtain the desired characteristics of the composition, such as the removal of the reverse-thermal gelation property as recited in claim 20, as disclosed by the secondary reference.

It would also have been obvious to one of ordinary skill in the art to have used the delivery system comprising 20 to 30 percent poloxamer and theory to deliver the active agents of the primary reference motivated by the desire to provide a sustained release composition that exist in a liquid form and gels when introduced into the body wherein the therapeutic composition is released over a period of time, as disclosed by the secondary reference.

Normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind. Experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233, 235 (CCPA 1955). It would also have been obvious to one of ordinary skill in the art to have adjusted the amount of N-acetylcysteine in the compositions of the primary reference motivated by the desire to deliver an effective amount of active agent to obtain optimal results as supported by cited precedent.

3) Claims 1, 15, 20, 22, 24-25, 35, 38, 137, 140 and 142-148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boggs (US 5,358,705) in view of Stratton et al. (US 5,861,174).

Boggs et al. disclose oral compositions for preventing conditions of the oral cavity. The active ingredients in the compositions include N-acetylcysteine complexes, which make up 0.05 to 10% of the compositions as recited in the instant claims. These concentrations are considered "safe and effective", which is defined as an amount of compound or composition sufficient to induce a significant positive modification in the condition being treated, but low enough to avoid serious side effects (col. 4, lines 11-32). The compositions also include surfactants such as Pluronic F-127 and make up 0 to 10% of the compositions. The reference differs from the instant claims insofar as it does not specifically disclose the compositions exhibit thermal-reversible behavior.

The secondary reference is discussed above and disclosed the thermal properties of polyoxyethylene and polyoxypropylene copolymers. It is used as a general teaching to show the surfactants used in the compositions of the primary reference are thermal responsive polymers and do not display thermal responsive gelation at the disclosed concentrations. The reference differs from the instant claims insofar as it does not disclose comprising N-acetylcysteine in the compositions.

It would have been obvious to one of ordinary skill in the art to have used the amounts of poloxamer used in the compositions of the primary reference motivated by the desire to inhibit gel formation but still has an increased viscosity when introduced

into the body to prolong the release of the active agent, as disclosed by the secondary reference.

Claims 1, 15, 17, 19-20, 22, 24-25, 31, 34, 38, 133-137 and 142-148 are rejected.

No claims allowed.

Conclusion

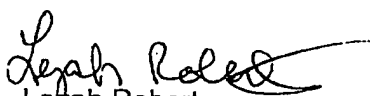
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

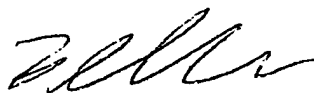
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Lezah Roberts
Patent Examiner
Art Unit 1614


Frederick Krass
Primary Examiner
Art Unit 1614

Declaration of Antony James Mathews
App. Serial No. 10/788,277

APPENDIX C
TO
DECLARATION
OF
ANTONY JAMES MATHEWS

Copy:

Dobrozsi et al. (US Patent No. 6,503,955)



US006503955B1

(12) United States Patent
Dobrozsi et al.(10) Patent No.: **US 6,503,955 B1**(45) Date of Patent: **Jan. 7, 2003****(54) POURABLE LIQUID VEHICLES****(75) Inventors:** Douglas Joseph Dobrozsi, Loveland, OH (US); Jerry William Hayes, II, Cincinnati, OH (US); Bjorn Olof Lindman, Lund (SE); Rouja Hristova Ivanova, Ilmenau (DE); Paschalis Alexandridis, East Amherst, NY (US)**(73) Assignee:** The Procter & Gamble Company, Cincinnati, OH (US)**(*) Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**(21) Appl. No.:** 09/658,813**(22) Filed:** Sep. 11, 2000**Related U.S. Application Data****(60)** Provisional application No. 60/153,260, filed on Sep. 11, 1999.**(51) Int. Cl.⁷** A61K 47/32; A61K 9/14**(52) U.S. Cl.** 514/772.4; 424/485; 424/486**(58) Field of Search** 424/426, 78, 177, 424/485, 486; 514/772.4**(56) References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Thurman K. Page**Assistant Examiner**—Blessing Fubara**(74) Attorney, Agent, or Firm**—Joan B. Cunningham; John M. Howell; Karen F. Clark**(57) ABSTRACT**

The present invention covers pourable liquid vehicles that can be combined with compositions, materials and substances. Among the benefits of such pourable liquid vehicles is the compositions are retained on the moistened surface for a period of time sufficient to allow compositions, materials and substances to act on said surface, resisting erosion or run-off from additional moisture being applied. Such pourable liquid vehicles have a number of utilities including but not limited to cleaning and treating surfaces of objects as well as biological or living organisms, including living creatures.

27 Claims, No Drawings

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POURABLE LIQUID VEHICLES

CROSS REFERENCE

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Serial No. 60/153,260, filed Sep. 11, 1999.

TECHNICAL FIELD

Concentrated levels of polyoxyalkylene block copolymers are useful in vehicles incorporated into products that are designed to deliver compositions, materials and substances to moistened surfaces and aqueous environment. Acquiring moisture during use, the vehicle becomes sufficiently transformed from a liquid to a gel-like form that provides a benefit to the user. For example, mucosal surfaces of the body contain sufficient water to allow the pourable liquid vehicle comprising concentrated polyoxyalkylene block copolymers to be effectively delivered to the desired site wherein the accompanying compositions, materials and substances tenaciously adhere to the moistened surfaces and resist dissolution or erosion by water or biological fluid. Such uses include, but are not limited to the delivery of personal health care compositions, formulations and compounds including, but not limited to, pharmaceuticals (OTC and prescription), nutrients and the like.

In the discipline of pharmaceutical compositions there are a wide variety of dosage forms. Examples include tablets, capsules, elixirs, syrups, liquid-filled capsules, suspensions, coated tablets or capsules for administration by mouth; gels, rinses, dentifrices, lozenges, sprays, medicated lollipops, liquid filled capsules for intra-oral administration; gels, suspensions or solutions for intra-ocular or intra-aural administration; suppositories and douches or enemas for intra-rectal or vaginal administration; and creams, ointments, gels, lotions and patches for topical application on the skin and scalp; and liquid suspension or solutions for injection by syringe, nasal gels, solutions, or suspensions for application into the nose with special applications or sprayers.

The majority of these compositions are in the physical form of a fluid having a viscosity ranging from pourable liquids to stiff gels. Pourable liquids are often preferred since they are in the best form to be administered. For example, only liquids, or perhaps low viscosity gels, can be injected through a syringe, or poured from a bottle into a medicine cup, or drawn up into a syringe or medicine dropper, or squeezed from a dropper bottle into the eye or ear, or atomized into the nasal cavities. In addition to the compatibility with pharmaceutical administration devices and with the mode of introduction into the body, it is often desirable for the composition to easily spread after application without the aid of manual action or devices. The eye drop compositions, for example, need to spread over the surface of the eye, as do swallowed liquids intended to coat the throat, esophagus, or stomach. This is similarly true of rectal enemas or vaginal douche compositions.

In many cases, however, pharmaceutical dosage forms in form of pourable liquids are not necessarily desirable since once administered, such pourable liquids are easily removed from the intended treatment site. In such circumstances the therapeutic advantage of the composition may be significantly diminished or even lost completely. It is appropriate, therefore, to surmise that for the purpose of being retained at the targeted site, it may be desirable for a particular pharmaceutical composition to be more viscous, even in the form of a gel that is not readily flowable. It is, however,

difficult or even impossible to administer such a viscous composition to its intended site to do the most good. For example, serious injury could occur when attempting to spread a gel on the surface of one's eye using a finger or more elaborate applicators. More problematic is coating the stomach lining, as this site is simply not accessible using simple self-administer applicators.

There is, therefore, a need for pharmaceutical compositions that are "smart"; that is, capable of being administered in a pourable liquid that are converted or transformed after administration into a vehicle having sufficient viscosity to essentially remain at the targeted site. Such compositions require a built-in chemical or physical triggering mechanism(s) that respond to conditions after application in or on a surface including the body.

BACKGROUND OF THE INVENTION

Attempts to develop such compositions have been ongoing for a significant period of time. Examples of such compositions include intra-ocular dosage forms as disclosed in Edsman, K., Carlfors, J., Petersson, R., *Rheological Evaluation of Poloxamer as an In Situ Gel for Ophthalmic Use*, European Journal of Pharmaceutics Vol. 6 pp.105-112 (1998) herein incorporated by reference. Compositions such as these are broadly described as primarily aqueous solutions of block co-polymer surfactants, other wise referred to as "poloxamers", that are commonly known in the art. When formulated in water as somewhat concentrated solutions, or with water and co-solvents, the poloxamer solution remains as a pourable liquid. The most commonly reported example of this type of system consists of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water. These compositions are administered at room temperature as liquids. They form a gel upon reaching body temperature. The trigger for converting these compositions to a gel, therefore, is body heat.

In situ gelation of pharmaceutical compositions based on poloxamer that are biologically triggered are known in the art. For example Kim, C. K., Lee, S. W., Choi, H. G., Lee, M. K., Gao, Z. G., Kim, I. S., and Park, K. M.: *Trials of In Situ Gelling and Mucoadhesive Acetaminophen Liquid Suppository in Human Subjects*, International Journal of Pharmaceutics vol. 174, pp. 201-207 (1998) incorporated herein by reference. Kim et al. discloses liquid suppositories for enhancing absorption of the pain and fever relieving drug acetaminophen.

U.S. Pat. No. 5,256,396, issued Oct. 26, 1993, to Colgate Palmolive Company, incorporated herein by reference, describes similar compositions containing poloxamer 407 and water at specified concentrations. Other products utilizing bio-triggers include those comprising poloxamer 407 at ranges preferably 12% to 17%. When combined with pharmaceutically active agents, these compositions are injected into the gingival space between the root of a tooth and the gum.

Poloxamers represent a large family of polymers that vary in molecular weight as well as in the percentage or portion of the block copolymer that is considered hydrophobic. Compositions comprising other poloxamers from this family having similar liquid/gelling characteristics are somewhat predictable, lacking only in the understanding of the required concentration of poloxamer. While there is a large number of uses for such compositions, they all rely on the same general mechanism of temperature-induced gelation of aqueous poloxamer dispersions. Compositions known in the art are found to be inadequate, however, as the gel structure readily dissolves in aqueous environments.

SUMMARY OF THE INVENTION

The present invention covers pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments. The benefits of compositions formulated with such pourable liquid vehicles include retention of the compositions, materials and substances on the moistened surface. This in turn allow for effective delivery of a desired composition, material and substance in the vehicle that acts on targeted surface, resisting erosion or run-off even in an aqueous environment. Such pourable liquid vehicles have a number of utilities for delivery of all kinds of materials including but not limited to cleaning and treating surfaces of objects as well as biological or living organisms, including living creatures.

Another object of this invention is to utilize such pourable liquid vehicles to deliver health care compositions and materials and substances to living creatures, particularly mammals, and most particularly humans. Even another object of the present invention is to develop a method for effective delivery of health care compositions, materials and substances.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Terms useful herein are defined below. Additionally, terms used in the art, as well as general concepts, are further described in Schramm, *The Language of Colloid and Interface Science*, American Chemical Society, (1993), incorporated herein by reference.

The term "pourable liquid" as used herein means the physical state of the compositions of the present invention prior to formation of a gel.

The term "moistened surface" as used herein means any living or non-living surface having sufficient moisture in or on it to trigger rapid conversion of a pourable liquid to a gel.

The term "in situ gelation" as used herein means the conversion of a pourable liquid to a gel at a designated site or surface.

As used herein, the term "gel" describes the substance resulting from the combination of the pourable liquid and water, or bodily fluid containing mostly water. The gel is sufficiently viscous to remain at the site applied to, or ultimately targeted for, over a period of time sufficient for the compositions, materials and substances in the gel to bring about a desired result at the site they are delivered to.

The term "triggering device" as used herein means a stimulus external to the composition that induces the conversion of a pourable liquid to a gel.

The term "shear" as used herein is the rate of deformation of a fluid when subjected to a mechanical shearing stress. In simple fluid shear, successive layers of fluid move relative to each other such that the displacement of any one layer is proportional to its distance from a reference layer. The relative displacement of any two layers divided by their distance of separation from each other is termed the "shear" or the "shear strain". The rate of change with time of the shear is termed the "shear rate".

A certain applied force is needed to produce deformation in a fluid. For a plane area around some point in the fluid and in the limit of decreasing area the component of deforming forces per unit area that acts parallel to the plane is the "shear stress".

The "viscosity" of a viscous material, also called viscosity index, is defined as the ratio of the shear stress applied into

the material, divided by the rate of shear which results. Materials of a higher viscosity have a higher resistance to flow, or to forces which can induce flow, than a lower viscosity material. All viscosities listed herein are at a shear rate of about 50 per second unless otherwise indicated. All of the rheologic characteristics given herein can be measured in a controlled rate or a controlled stress rotational viscometer capable of some operation in a controlled rate mode, for Example Haake RS 150 by Haake GmbH, Karlsruhe, Germany; Carrimed CSL 500 Controlled Stress Rheometer by TA Instruments, New Castle, Delaware; and Rheometric SRS, by Rheometric Scientific, Piscataway, N.J.

Specifically, when subject to constant shearing rate of about 50 per second at normal ambient temperature (approx. 25° C.), the present liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds.

The value of a composition's triggered viscosity ratio ("T") is useful in determining the degree to which a composition exhibits the above described gelling characteristic. The formula and procedure for determining the triggered viscosity ratio is set forth below.

It is desirable for the compositions of the present invention to exhibit a triggered viscosity ratio of at least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10 wherein the triggered viscosity is defined by the following formula or ratio:

$$T = \eta_g / \eta_f$$

where η_g = viscosity of the gel and

where η_f = viscosity of the pourable liquid

The pourable liquid vehicle of the present invention must be selected and formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture. Examples of these fluids are saliva, gastric fluid, intestinal fluid, extracellular fluid present under the skin at the site of a subcutaneous injection, or in muscle tissue at the site of an intramuscular injection, cerebrospinal fluid, vaginal fluid, fluid exudate from an open wound or ulcer, tear fluid, rectal fluid, or any other bodily fluid of an animal which contains in large measure water. In other words, after the pourable liquid vehicle contacts with the bodily fluid, the viscosity of the pourable liquid vehicle becomes greater than the viscosity of either the pourable liquid vehicle itself prior to mixing, or the bodily fluid alone.

The triggered viscosity ratio of a pourable liquid vehicle can be determined by one skilled in the art using appropriate viscosity measuring instruments, and is exemplified by the following method. First, the viscosity of the pourable liquid vehicle (η_f) is determined in a rheometer using a shear rate of 50 per second at 25° C. For the determination of η_g , 1 ml of the pourable liquid vehicle is placed onto the plate of a Haake RS 150 rheometer. The temperature is controlled in the range of typical room temperature, about 25° C. A cover is used on the measuring system and a solvent-saturated atmosphere provided to prevent evaporation of water, ethanol, or other volatile components from the sample during the test. A 35 mm diameter parallel plate measuring system is lowered onto the sample, leaving a gap of about 1 millimeter, and an equilibration shearing of approximately 10 per second is applied for 10 seconds. Then, a constant shearing rate of 50 per second is applied for 30 seconds. The viscosity η_g is read from the instrument at the 30 second time point.

For the determination of η_p , two dilutions of the pourable liquid vehicle are made with water. The first dilution is made to contain 75% by weight of the pourable liquid vehicle, and 25% by weight of additional water. The second dilution is made to contain 50% by weight of pourable liquid vehicle and 50% by weight of additional water. The pourable liquid vehicle and water are combined in a vial and a tight seal applied to prevent evaporation of components. The vial contents are mixed in an unusual manner, by repeated centrifugation. This is necessary since some of the combinations are very viscous gels. Specifically, the vials are centrifuged (using for example a Beckman GS-6R centrifuge, available from Beckman Instruments, Palo Alto, Calif.) 20 minutes at 3000 RPM and 25° C. for at least four separate centrifuge runs. After each run the vials are inverted. Additional runs are conducted in the centrifuge to ensure complete mixing. 1 ml of the gelled sample is then loaded onto the plate of the same rheometer used for the measurement of η_p , except that the temperature is controlled at the normal body temperature of a human, 37° C. An identical rheometer measurement program is used as for determination of η_p . The triggered viscosity factor for both the 25% and 50% dilution of the sample is calculated from η_p and η_g as described by the formula above. These two dilutions have been found to be useful for measuring the gelling functionality of the pourable liquid vehicles of the invention in a standardize method, because some of the pourable liquid vehicles may require a greater or lesser amount of water in order to trigger the gelling character. The use of other water dilutions for determination of η_p , ranging from about 5% up to about 70%, would also be expected to provide a demonstration of the unique, gelling character of the invention, but the dilution which yields a maximal value of T varies depending upon the exact pourable liquid vehicle being tested.

All percentages of the components comprising the invention are herein referred to their weight in the pourable liquid vehicle as a whole.

The present invention is a pourable liquid vehicle comprising:

(a) from about 26% to about 100% polyoxyalkylene block copolymer;

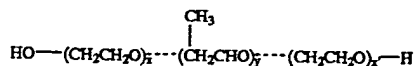
(b) from about 0% to about 70% glycol; and

(c) from about 0% to about 50% water;

wherein said vehicle is used to deliver compositions, materials and substances to moistened surfaces and aqueous environments said vehicle has a viscosity value η_p less than or equal to 7 pascal-seconds and the value T greater than or equal to about 1.3.

Polyoxyalkylene Block Copolymer

Polyoxyalkylene block copolymers herein referred to as "poloxamers" are nonionic block copolymers of ethylene oxide and propylene oxide corresponding to the following structure:



wherein x, y, and x' have a value wherein the pourable liquid vehicle has a viscosity value η_p less than or equal to 7 pascal-seconds and the value T greater than or equal to about 1.3. Preferable polyoxyalkylene block copolymers useful in the present invention include wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, wherein the average molecular weight of said copolymer is from about 3000 to

about 15,000. More preferred is wherein x equals 37, y equals 58, and x' equals 37, and the copolymer has an average molecular weight of about 6500. Most preferred is wherein x equals 100, y equals 70, and x' equals 100, and the copolymer has an average molecular weight of about 12,600.

The poly(oxyethylene) segment is hydrophilic and the poly(oxypropylene) segment is hydrophobic. The level of the poloxamers useful in the present invention ranges from about 26% to about 100%, preferably from about 27.8% to about 95%, more preferably 30% to about 90% by weight of the pourable liquid vehicle. In other words, providing the poloxamer has the critical viscosities above, it can be used itself or when combined with other compositions, materials and substances.

A family of poloxamers are available and vary in the number of blocks, the overall average molecular weight, and in the percentage of the molecule which is hydrophilic. A block refers to a single polyoxyethylene or polyoxypropylene segment. Di-block and tri-block polymers have been described. In the case of tri-block copolymers, the blocks can be arranged in the format of one polyoxypropylene block surrounded by 2 polyoxyethylene blocks, that being the most common poloxamer structure, or alternatively as one polyoxyethylene block surrounded by 2 polyoxypropylene blocks, the latter sometimes referred to as a reverse poloxamer. Poloxamers are available under the trade names of Lutrol, Monolan, or Pluronic. The chemical structure, synthesis, and properties have been described [(poly(ethylene oxide)/poly(propylene oxide)) block copolymer surfactants, Paschalis Alexandridis, *Current Opinions in Colloid and Interface Science*, Vol 2, pp. 478-489 (1997) herein incorporated by reference.

For applications in the health care area, compositions embodying the present invention utilize a specific group of pharmaceutically acceptable block copolymers or poloxamers. These poloxamers are selected from the group consisting of Pluronic F127, P105, F108 and mixtures thereof, all available from BASF Corp.

Glycols

In addition to the poloxamers, it is desirable in some of the pourable liquid vehicles of the present invention to combine glycols with the poloxamers for controlling the viscosity of the pourable liquid vehicles. These glycols permit the pourable liquid vehicle to remain pourable while containing very high levels of the poloxamer so that administration is convenient, or so that the composition can readily pass through the bore of a syringe or other dosing apparatus. Additionally, these glycols provide solvent capacity for pharmaceutical actives or other composition components. The level of glycols in the present invention is from 0% to about 70%, preferably from about 10% to about 70% and most preferably from about 7% to about 62% of the pourable liquid vehicle.

Glycols are low molecular weight polyols and are selected from the group consisting of monosaccharides such as glucose (dextrose), fructose (levulose); disaccharides such as sucrose, lactose, maltose, cellobiose and other sugars, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, ethanol, honey, mannitol, polyethylene glycol, glycerol and mixtures thereof. Preferred glycols are selected from the group consisting of ethanol, glycerol and propylene glycol, and mixtures thereof. Absolute ethanol is available from Aaper Alcohol & Chemical Co., Shelbyville, Ky.

Water

In addition to the poloxamers, and, or the glycol, it is desirable in some of the pourable liquid vehicles of the

present invention to include water. Water is useful at a level from 0% to about 50%, preferably about 1% to about 46%, most preferably from about 2% to about 41% of the pourable liquid vehicle.

Preferred Embodiments

Preferred embodiments of the present invention utilizing the combination of poloxamers, polyols and water include the following:

1. from about 26% to about 65% Pluronic F127, from about 22% to about 38% ethanol and from about 8% to about 45% water.
2. from about 52% to about 60% Pluronic F108, from about 20% to about 25% ethanol and from about 17% to about 27% water.
3. from about 25% to about 50% Pluronic P105, from about 45% to about 65% propylene glycol and from about 5% to about 20% water.
4. from about 37% to about 77% Pluronic P105, from about 12% to about 28% ethanol, and from about 10% to about 45% water.
5. from about 26% to about 49% Pluronic F127, from about 2% to about 12% ethanol, from about 30% to about 68% propylene glycol, and from about 7% to about 40% water.

Materials to be Delivered

As previously stated, the pourable liquid vehicles of the present invention are useful as delivery vehicles for desired compositions, materials and substances that may be dispersed into them. This could range from compositions, materials and substances that are desired to remain on an applied surface for a period of time to deliver a benefit. Examples include antimicrobials for cleansing surfaces including sinks, toilets and shower tile; to body wounds; oral treatment of gingival and buccal tissues as well as teeth surfaces; agricultural uses including elimination of undesirable plants, animals, viruses, bacteria insects, and the like.

The present invention is particularly useful for the delivery of health care compositions, materials, and substances. These materials can range from dietary compositions to promote nutrition or weight loss to pharmacologically effective amounts of agents selected from the group consisting of antibacterial substances, antihistamines, antitussives, anti-inflammatories, expectorants/mucolytics, mast cell stabilizers, leukotriene antagonists, methylxanthines, antioxidants, steroids, bronchodilators, antivirals, biologics, analgesics, anesthetics, antiarthritics, antiasthmatics, urinary tract disinfectives, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, muscle relaxants, antiprotozoals, and mixtures thereof.

Preferred embodiment of the present invention relates to compositions including pharmaceutically acceptable polyoxyalkylene block copolymer and glycols in combination with a pharmacologically active agent. Suitable classes of agents that can be administered by embodiments of the present invention include:

Antibacterial substances such as β -lactam antibiotics, such as cefoxitin, n-formamidoyl thienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides; aminoglycoside antibiotics such as gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acids and analogs such as norfloxacin and the antimicrobial combination of fluoroalanine/pentizidone; nitrofurazones, and mixtures thereof.

Antihistamines, including, Hydroxyzine, Pyrilamine, Phenindamine, Dexchlorpheniramine, Clemastine

Diphenhydramine, Azelastine, Acrivastine, Levocabastine, Mequitazine, Astemizole, Ebastine, Loratadine, Cetirizine, Terfenadine, Promethazine, Dimenhydrinate, Meclizine, Tripelemamine, Carbinoxamine, Cyproheptadine, Azatadine, Brompheniramine, Triprolidine, Cyclizine, Thonzylamine, Pheniramine, and mixtures thereof.

Antitussives, including, Hydrocodone, Noscapine, Benzonatate, Diphenhydramine, Chlophedianol, Clobutinol, Fominoben, Glauicine, Pholcodine, Zipeprol, Hydromorphone, Carbetapentane, Caramiphen, Levopropoxyphene, Codeine, Dextromethorphan, and mixtures thereof.

Antiinflammatories preferably Non-Steroidal Anti-inflammatories (NSAIDS) including, Ketoprofen, Indoprofen, Indomethacin, Sulindac, Diflunisal, Ketorolac, Piroxicam, Meclofenamate, Benzydamine, Carprofen, Diclofenac, Etodolac, Fenbufen, Fenoprofen, Flurbiprofen, Mefenamic, Nabumetone, Phenylbutazone, Pirofen, Tolmetin, Ibuprofen, Naproxen, Sodium naproxen, Aspirin, and mixtures thereof.

Expectorants/Mucolytics, including, Ambroxol, Bromhexine, Terpin, Guaifenesin, Potassium iodide, N-Acetylcysteine, and mixtures thereof.

Mast Cell Stabilizers, preferably intranasally, or orally administered mast cell stabilizers, including, Cromoglyn, Oxatamide, Ketotifen, Lodoxamide, Nedocromil, and mixtures thereof.

Leukotriene Antagonists, including, Zileuton and others.

Methylxanthines, including, Caffeine, Theophylline, Enprofylline, Pentoxifylline, Aminophylline, Dyphylline, and mixtures thereof.

Antioxidants or radical inhibitors, including, Ascorbic acid, Tocopherol, Pycnogenol, and mixtures thereof.

Steroids, preferably intranasally administered steroids, including, Beclomethasone, Fluticasone, Budesonide, Mometasone, Triamcinolone, Dexamethasone, Flunisolide, Prednisone, Hydrocortisone and mixtures thereof.

Bronchodilators, preferably for inhalation, including, Albuterol, Epinephrine, Ephedrine, Metaproterenol, Terbutaline, Isoetharine, Terbutaline, Isoetharine, Pirbuterol, Bitolterol, Fenoterol, Rimiterol, Ipratropium, and mixtures thereof.

Antivirals, including, Amantadine, Rimantadine, Enviroxime, Nonoxinols, Acyclovir, Alpha-Interferon, Beta-Interferon, and mixtures thereof.

Biologics, including, cytokine and celladhesion molecule inhibitors, ICAM antagonists, interleukin agonists or antagonists, hormones, polypeptides, amino acids, nucleotides, antibodies, and mixtures thereof.

Analgesics such as aspirin, acetaminophen, diflunisal, and mixtures thereof. Anesthetics such as lidocaine, procaine, benzocaine, xylocaine, and mixtures thereof.

Antiarthritics such as phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone, probenecid, and mixtures thereof.

Antiasthma drugs such as theophylline, ephedrine, beclomethasone dipropionate, epinephrine, and mixtures thereof.

Urinary tract disinfectives such as sulfamethoxazole, trimethoprim, nitrofurantoin, norfloxacin, and mixtures thereof.

Anticoagulants such as heparin, bishydroxycoumarin, warfarin, and mixtures thereof.

Anticonvulsants such as diphenylhydantoin, diazepam, and mixtures thereof.

Antidepressants such as amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine, doxepin, and mixtures thereof.

Antidiabetics such as insulin, tolbutamide, tolazamide, acetohexamide, chlorpropamide, and mixtures thereof.

Antineoplastics such as adriamycin, fluorouracil, methotrexate, asparaginase, and mixtures thereof.

Antipsychotics such as prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, triflupromazine, and mixtures thereof.

Antihypertensive such as spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propranolol, metoprolol, prazosin hydrochloride, reserpine, and mixtures thereof.

Muscle relaxants such as melphalan, dantrolene, cyclobenzaprine, methocarbamol, diazepam, and mixtures thereof.

Antiprotozoals such as chloramphenicol, chloroquine, trimethoprim, sulfamethoxazole, and mixtures thereof.

For treatment of vaginal and urethral conditions requiring antifungal, amoebicidal, trichomonocidal agents or antiprotozoals, the following agents can be used: polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfanilamide, candicidin, sulfoxazole, nystatin, clotrimazole, metronidazole and mixtures thereof; antiprotozoals such as chloramphenicol, chloroquine, trimethoprim, sulfamethoxazole and mixtures thereof; antiviral effective compounds such as acyclovir and interferon. Spermicidal can be used such as nonoxynal.

EXAMPLES

Example I

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	1.47
Vehicle ¹	98.18
Sodium Saccharin	0.3
Monoammonium Glycerizinnate	0.05
Flavors and Colors	Flavors and Colors

¹Vehicle contains (w/w %):

Pluronic F127	55.51%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	26.48%
Water	18.01%

Preparation

Add the dextromethorphan base, sodium saccharin, and monoammonium glycerizinnate into a clean vessel. Add ethanol and then the poloxamer and water. Mix until clear and uniform.

Example II

Composition for the Treatment of Cough and Decongestion

Component	% (w/w)
Dextromethorphan Base	1.47
Chloropheniramine Maleate	0.26
Vehicle ¹	97.92
Sodium Saccharin	0.3

-continued

Component	% (w/w)
Monoammonium Glycerizinnate	0.05
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):

Pluronic F127	55.66%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	26.55%
Water	17.79%

Preparation

- 15 Mill and screen the menthol and tienzoocaine to reduce the product particle size. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycerizinnate into a clean vessel. Add eucalyptus oil, ethanol to the vessel. Subsequently add the poloxamer and water to the vessel.
- 20 Mix until uniform.

Example III

Demulcent Composition for the Treatment of Sore Throat

Component	% (w/w)
Vehicle ¹	96.845
Menthol	1.00
Benzocaine	2.00
Eucalyptus Oil	0.005
Sodium Saccharin	0.10
Monoammonium Glycerizinnate	0.05
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):

Pluronic F108	56.79%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Ethanol	21.69%
Water	21.52%

Preparation

- 45 Mill and screen the menthol and benzocaine to reduce the product particle size. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycerizinnate into a clean vessel. Add eucalyptus oil, ethanol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example IV

Composition for the Rectal Delivery of Acetaminophen

Component	% (w/w)
Vehicle ¹	95.0
Acetaminophen	5.0

¹Vehicle contains (w/w %):

Pluronic P105	44.21%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Propylene Glycol	52.63%
Water	3.16%

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Preparation

Mill and screen the acetaminophen to reduce the particle size. Add the acetaminophen into a clean vessel. Add propylene glycol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example V

Composition for the Topical Delivery of an Analgesic

Component	% (w/w)
Vehicle ¹	98.0
Ketoprofen	2.0
Perfumes	As Desired

¹Vehicle contains (w/w %):

Pluronic F127	56.12%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	30.61%
Water	13.27%

Preparation

Screen the ketoprofen to reduce the particle size. Add the ketoprofen into a clean vessel. Add ethanol to the vessel. Subsequently add poloxamer and water to the vessel. Mix until uniform.

Example VI

Composition for the Topical Delivery of an Analgesic

Component	% (w/w)
Vehicle ¹	95.0
Ibuprofen	5.0
Perfumes	As Desired

¹Vehicle contains (w/w %):

Pluronic P105	63.16%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	18.95%
Water	17.89%

Preparation

Screen the ibuprofen to reduce the particle size. Add the ibuprofen into a clean vessel. Add ethanol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example VII

Composition for the Delivery of an Oral Antimicrobial

Component	% (w/w)
Vehicle ¹	98.57
Triclosan Monophosphate	0.28
Menthol	1.00
Sodium Saccharin	0.10
Monammonium Glycerizinnate	0.05

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-continued

Component	% (w/w)
Flavors and Colors	As Desired

¹Vehicle contains (w/w %):

Pluronic F108	55.80%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	21.30%
Water	22.90%

Preparation

Mill and screen the menthol and triclosan monophosphate to reduce particle size. Add the menthol, triclosan monophosphate, sodium saccharin, and monoammonium glycerizinnate into a clean vessel. Add propylene glycol to the vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Example VIII

Composition for the Intranasal Delivery of a Decongestant

Component	% (w/w)
Vehicle ¹	99.32
Oxymetazoline HCl	0.05
Tyloxapol	0.15
Dibasic Sodium Phosphate	0.04
Monobasic Potassium Phosphate	0.13
Benzalkonium Chloride	0.04
Chlorhexidine Gluconate	0.26
Disodium EDTA	0.01

¹Vehicle contains (w/w %):

Pluronic F127	40.27%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	26.18%
Water	33.55%

Preparation

Add the dibasic sodium phosphate, monobasic potassium phosphate, disodium EDTA, benzalkonium chloride and oxymetazoline HCl into a clean vessel. Add tyloxapol, chlorhexidine gluconate, and ethanol to the vessel. Subsequently add, the poloxamer and water to the vessel. Mix until uniform.

Example IX

Composition to Vaginally Deliver Hormonal Replacement Therapy

Component	% (w/w)
Vehicle ¹	99.99
Beta Estradiol	0.01
Perfumes	As desired

¹Vehicle contains (w/w %):

Pluronic P105	45.00%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Propylene glycol	48.00%
Water	7.00%

Preparation

Add the beta estradiol and propylene glycol into a clean vessel. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

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Example X

Composition for the Rectal Delivery of an Antiemetic

Component	% (w/w)
Vehicle ¹	99.75
Promethazine HCl	0.25

¹Vehicle contains 100.0% (w/w %) Pluronic L62 (BASF Specialty Chemicals, Mount Olive, N.J.)

Preparation

Mill and screen the promethazine HCl to reduce particle size. Add the poloxamer and the Promethazine HCl into a clean vessel. Mix until uniform.

Example XI

Composition for the Rectal Delivery of an Antiemetic

Component	% (w/w)
Vehicle ¹	98.75
Carbomer ²	1.00
Promethazine HCl	0.25

¹Vehicle contains 100.0% (w/w %) Pluronic L62 (BASF Specialty Chemicals, Mount Olive, N.J.)

²Carbopol 974 available from B. F. Goodrich Company, Brecksville, Ohio

Preparation

Mill the promethazine HCl to reduce particle size. Sieve the carbomer and promethazine HCl and add to a clean vessel. Add the poloxamer. Mix until uniform.

Example XII

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40
Monoammonium Glycerizinnate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

Pluronic F127 33.56%
(BASF Specialty Chemicals, Mount Olive, N.J.)

Ethanol 10.51%

Water 13.42%

Propylene glycol 42.51%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dex-

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tromethorphan base and monoammonium glycerizinnate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

5 Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

10 The preparation has a viscosity (η_p) of 0.67 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 10.5.

Example XIII

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40
Monoammonium Glycerizinnate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

30 Pluronic F127 29.08%
(BASF Specialty Chemicals, Mount Olive, N.J.)

Ethanol 10.51%

Water 24.61%

Propylene glycol 35.80%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glycerizinnate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

45 Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

50 The preparation has a viscosity (η_p) of 0.97 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 4.95.

Example XIV

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	95.15
Sodium Metabisulfite	0.10
Disodium EDTA	0.10
Sodium Saccharin	0.40

-continued

Component	% (w/w)
Monoammonium Glycerizinate	0.15
Acesulfame	0.50
Flavor	1.40

¹Vehicle contains (w/w %):

Phuronic F127	40.27%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.51%
Water	13.42%
Propylene glycol	35.80%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, dextromethorphan base and monoammonium glycerizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

The preparation has a viscosity (η_p) of 2.14 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 6.05.

Example XV

Composition for the Treatment of Cough

Component	% (w/w)
Dextromethorphan Base	2.20
Vehicle ¹	97.8
Flavors	As desired

¹Vehicle contains (w/w %):

Pluraflo 1220	40.90%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.22%
Propylene Glycol	46.83%
Anhydrous glycerine	2.05

Preparation

Weigh the dextromethorphan into a clean vessel, add the ethanol and begin mixing. Add propylene glycol and mix until uniform and clear. Add Pluraflo and mix. Add glycerin and mix until uniform. Subsequently, add desired flavor component and mix until uniform.

The proportions of poloxamer:glycol in the preparation is 40.90:59.10.

Example XVI

Composition for the Treatment of Otitis

Component	% (w/w)
ofloxacin	0.30
Vehicle ¹	98.95
Perfume	0.75

¹Vehicle contains (w/w %):

Pluraflo 1220	45.48%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	5.05%
Propylene Glycol	41.23%
Anhydrous glycerine	8.24

Preparation

Add propylene glycol, Pluraflo, glycerine and ethanol to a clean vessel. While stirring, add ofloxacin. Stir until a clear solution is obtained. Subsequently, add perfume and mix until uniform.

Example XVII

Composition for the Treatment of Glaucoma

Component	% (w/w)
Timolol maleate	0.25
Vehicle ¹	99.75

¹Vehicle contains (w/w %):

Pluraflo 1220	92.73%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	2.11%
Anhydrous glycerine	5.16

Preparation

Add glycerine, ethanol and Pluraflo to a clean vessel. Add Timolol. Cover tightly and stir until a clear solution is obtained.

Example XIII

Composition for the Treatment of Ulcers

Component	% (w/w)
Omeprazole (Free Base)	2.00
Vehicle ¹	95.89
Sodium Metabisulfite	0.10
Sodium EDTA	0.10
Sodium Saccharin	0.25
Monoammonium Glycerizinate	0.11
Acesulfame	0.35
Flavor	1.20

¹Vehicle contains (w/w %):

Phuronic F127	34.07%
(BASF Specialty Chemicals, Mount Olive, N.J.)	
Ethanol	10.43%
Water	13.32%
Propylene glycol	42.18%

Preparation

Add propylene glycol and poloxamer to a clean vessel (main mix). While stirring, heat the mixture as appropriate

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to sufficiently melt the poloxamer. Once a uniform solution is obtained remove from heat source and continue mixing. In a separate vessel (alcohol pre-mix) add alcohol, omeprazole base and monoammonium glycerizinate and mix until uniform. In another vessel (water pre-mix), add water, EDTA, sodium saccharin, acesulfame and sodium metabisulfite. Mix until all materials are dissolved.

Add the alcohol containing premix to the main mixing vessel containing the poloxamer. Mix until uniform. While stirring, add the water containing premix to the main vessel and continue to mix until uniform. Subsequently, add desired flavor component and mix until uniform.

Example XIX

Composition for the Controlled Release of an Appetite Suppressant

Component	% (w/w)
Phenylpropanolamine Vehicle ¹	3.3
Sodium Metabisulfite	96.5
Disodium EDTA	0.10

¹Vehicle contains (w/w %):

Pluraflo 1220	70.12%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Propylene glycol	11.27
Ethanol	2.26%
Anhydrous glycerine	16.35

Preparation

Add alcohol, propylene glycol, EDTA, sodium metabisulfite and phenylpropanolamine to a clean vessel and begin mixing. Subsequently, add, Pluraflo and glycerine to the vessel. Mix until uniform.

This liquid may be filled into hard gelatin capsules that are then banded to prevent leakage, or it may be used as the fill for a soft elastic gelatin capsule. One capsule is made to contain 0.75 ml of the liquid, and taken 3 times daily provides controlled release of the phenylpropanolamine active. After swallowing, the gelatin shell dissolves in the gastrointestinal tract and the liquid fill immediately transforms in to a slow dissolving gel that provides controlled release of the phenylpropanolamine.

Example XX

Composition for the Injection of an Analgesic

Component	% (w/w)
Morphine Sulfate Vehicle ¹	1.0
	99.0

¹Vehicle contains (w/w %):

Pluraflo 1220	52.63%
	(BASF Specialty Chemicals, Mount Olive, N.J.)
Propylene glycol	35.79%
Ethanol	3.16%
Anhydrous glycerine	8.42%

Preparation

Add propylene glycol, ethanol, glycerine and morphine sulfate into a clean vessel and begin mixing. Subsequently, add poloxamer (Pluraflo) and mix until uniform.

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The composition provides pain relief when 1 mL is injected intramuscularly.

What is claimed is:

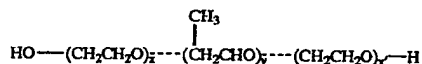
1. A pourable liquid vehicle comprising:

(a) from about 26% to about 97% by weight of a polyoxyalkylene block copolymer;

(b) from about 2% to about 70% by weight of a glycol; and

(c) from about 1% to about 50% by weight of water; wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, wherein said vehicle has a viscosity value η_f less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3, and wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the glycol of from about 1:0.16 to about 1:2.20, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the glycol to the water of from about 1:0.08 to about 1:4.25.

2. The pourable liquid vehicle according to claim 1 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3,000 to about 15,000.

3. The vehicle according to claim 2 comprising from about 27.8% to about 95% of the polyoxyalkylene block copolymer wherein said vehicle has a viscosity η_f less than or equal to 2 pascal-seconds and value T is greater than or equal to about 2.

4. The vehicle according to claim 2 comprising from about 30% to about 90% of the polyoxyalkylene block copolymer wherein said vehicle has a viscosity η_f less than or equal to 2 pascal-seconds and value T is greater than or equal to about 5.

5. The vehicle according to claim 1 comprising from about 10% to about 70% by weight of the glycol.

6. The vehicle according to claim 5 wherein said glycol is selected from the group consisting of monosaccharides, disaccharides, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, honey, mannitol, polyethylene glycol, glycerol, and mixtures thereof.

7. The vehicle according to claim 1 comprising from about 1% to about 46% by weight of water.

8. The vehicle according to claim 2 comprising:

(a) from about 26% to about 65% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;

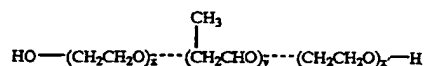
(b) from about 22% to about 38% by weight of the glycol; and

(c) from about 8% to about 45% by weight of water.

9. The vehicle according to claim 2 comprising:

(a) from about 25% to about 50% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;

- (b) from about 45% to about 65% by weight of the glycol; and
- (c) from about 5% to about 20% by weight of water.
10. The vehicle according to claim 2 comprising:
- (a) from about 52% to about 60% by weight of the polyoxyalkylene block copolymer wherein x is equal to 128, y is equal to 58, and x' is equal to 128, and the average molecular weight of the polyoxyalkylene block copolymer is about 14,600;
- (b) from about 20% to about 25% by weight of the glycol; and
- (c) from about 17% to about 27% by weight of water.
11. The vehicle according to claim 2 comprising:
- (a) from about 37% to about 77% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;
- (b) from about 12% to about 28% by weight of the glycol; and
- (c) from about 10% to about 45% by weight of water.
12. The vehicle according to claim 2 comprising:
- (a) from about 26% to about 49% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;
- (b) from about 30% to about 68% by weight of the glycol; and
- (c) from about 2% to about 12 % by weight of ethanol; and
- (d) from about 7% to about 40% by weight of water.
13. A method for delivery of pharmacologically active agents to mammals by administering the pourable liquid vehicle of claim 1 to a moistened site on or in said mammal wherein said vehicle has a viscosity η , less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.4.
14. The vehicle according to claim 1 wherein said compositions, materials, and substances are dietary compositions, pharmacologically active agents, or antimicrobials.
15. The vehicle according to claim 9 wherein the glycol is propylene glycol.
16. The vehicle according to claim 12 wherein the glycol is propylene glycol.
17. The vehicle according to claim 6 wherein the said vehicle further comprises from about 2% to about 70% by weight of ethanol, wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the ethanol of from about 1:0.16 to about 1:2.2, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the ethanol to the water of from about 1:0.08 to about 1:4.25.
18. A pourable liquid vehicle comprising:
- (a) from about 26% to about 100% by weight of a polyoxyalkylene block copolymer; and
- (b) from 0% to about 70% by weight of a glycol; wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, and wherein said vehicle has a viscosity value η , less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3.
19. The pourable liquid vehicle according to claim 18 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3,000 to about 15,000.

20. The pourable liquid vehicle according to claim 18 wherein the glycol is selected from the group consisting of monosaccharides, disaccharides, ribose, glycerin, sorbitol, xylitol, inositol, propylene glycol, galactose, mannose, xylose, rhamnose, glutaraldehyde, invert sugars, honey, mannitol, polyethylene glycol, glycerol, and mixtures thereof.

21. The pourable liquid vehicle according to claim 20 wherein said vehicle further comprises from 0% to about 70% by weight of ethanol.

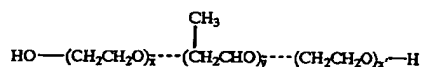
22. A pourable liquid vehicle comprising:

(a) from about 26% to about 97% by weight of a polyoxyalkylene block copolymer;

(b) from about 2% to about 70% by weight of ethanol; and

(c) from about 1% to about 50% by weight of water; wherein said vehicle is used to deliver compositions, materials, and substances to moistened surfaces and aqueous environments, wherein said vehicle has a viscosity value η , less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.3, and wherein said vehicle comprises weight ratios of the polyoxyalkylene block copolymer to the ethanol of from about 1:0.16 to about 1:2.2, the polyoxyalkylene block copolymer to the water of from about 1:0.10 to about 1:2.0, and the ethanol to the water of from about 1:0.08 to about 1:4.25.

23. The pourable liquid vehicle according to claim 22 wherein the polyoxyalkylene block copolymer corresponds to the following structure:



wherein x has a value from about 1 to about 130, y has a value from about 1 to about 72, and x' has a value from 0 to about 130, and wherein the polyoxyalkylene block copolymer has an average molecular weight of from about 3000 to about 15,000.

24. The vehicle according to claim 23 comprising:

(a) from about 26% to about 65% by weight of the polyoxyalkylene block copolymer wherein x is equal to 100, y is equal to 70, and x' is equal to 100, and the average molecular weight of the polyoxyalkylene block copolymer is about 12,600;

(b) from about 22% to about 38% by weight of the ethanol; and

(c) from about 8% to about 45% by weight of water.

25. The vehicle according to claim 23 comprising:

(a) from about 52% to about 60% by weight of the polyoxyalkylene block copolymer wherein x is equal to 128, y is equal to 58, and x' is equal to 128, and the average molecular weight of the polyoxyalkylene block copolymer is about 14,600;

(b) from about 20% to about 25% by weight of the ethanol; and

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(c) from about 17% to about 27% by weight of water.
26. The vehicle according to claim 23 comprising:

(a) from about 37% to about 77% by weight of the polyoxyalkylene block copolymer wherein x is equal to 37, y is equal to 58, and x' is equal to 37, and the average molecular weight of the polyoxyalkylene block copolymer is about 6,500;

(b) from about 12% to about 28% by weight of the ethanol; and

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(c) from about 10% to about 45% by weight of water.

27. A method for delivery of pharmacologically active agents to mammals by administering the pourable liquid vehicle of claim 22 to a moistened site on or in said mammal wherein said vehicle has a viscosity η , less than or equal to 7 pascal-seconds and a value T greater than or equal to about 1.4.

* * * * *

Declaration of Antony James Mathews
App. Serial No. 10/788,277

APPENDIX D
TO
DECLARATION
OF
ANTONY JAMES MATHEWS

Copy of Claims Considered

1. A therapeutic composition useful for treatment of oral mucositis as a side effect of cancer therapy, the composition comprising:

N-acetylcysteine in an amount effective as formulated in the composition to provide therapeutic effect for treatment of the mucositis;

from 5 weight percent to 20 weight percent poloxamer 407;

a carrier liquid comprising water in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart reverse-thermal viscosity behavior to the therapeutic composition, wherein the composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C;

wherein, at some temperature in a range of from 2°C to 8°C the therapeutic composition is in the form of an aqueous solution with the poloxamer 407 and the N-acetylcysteine dissolved in the water.

15. The therapeutic composition of Claim 1, wherein the N-acetylcysteine comprises from about 0.001 percent by weight to about 50 percent by weight of the composition.

17. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C to 20°C.

19. The therapeutic composition of Claim 1, wherein the biocompatible polymer, as formulated in the therapeutic composition, imparts a reverse-thermal gelation property to the composition with the composition having a reverse-thermal liquid-gel transition temperature within a range of from 1°C to 37°C, so that the therapeutic composition gels as the temperature of the therapeutic composition is increased from below to above the reverse-thermal gel transition temperature.

20. (Previously Presented) The therapeutic composition of Claim 1, wherein the amount of the water, as formulated in the composition, does not interact with the poloxamer 407 to impart reverse-thermal gelation properties to the composition.

22. The therapeutic composition of Claim 1, wherein the poloxamer 407 comprises from 5 weight percent to 20 weight percent of the composition.
24. The therapeutic composition of Claim 1, wherein the poloxamer 407 is dissolved in the water when the composition is at a temperature of 5°C.
25. The therapeutic composition of Claim 24, wherein the N-acetylcysteine is dissolved in the water when the composition is at a temperature of 5°C.
31. The therapeutic composition of Claim 1, comprising a bioadhesive agent that is different than the N-acetylcysteine and the poloxamer 407.
35. The therapeutic composition of Claim 1, comprising at least one taste masking component.
38. The therapeutic composition of Claim 1, comprising at least one preservative component.
133. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 60cP to at least about 70cP when a temperature of the composition is increased from 1°C to 37°C.
134. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 60cP to at least about 80cP when a temperature of the composition is increased from 1°C to 37°C.
135. The therapeutic composition of Claim 1, wherein the therapeutic composition exhibits an increase in viscosity from no larger than about 50cP to at least about 70cP when a temperature of the composition is increased from 1°C to 37°C.
136. The therapeutic composition of Claim 1, wherein the composition comprises reverse-thermal gelation properties with a reverse-thermal liquid-gel transition temperature within the range of temperatures.
137. The therapeutic composition of Claim 1, wherein the therapeutic composition comprises from 0.1 to 20 weight percent of the N-acetylcysteine.

140. The method of Claim 137, wherein the therapeutic composition comprises about 10 weight percent of the N-acetylcysteine.

142. The therapeutic composition of Claim 1, wherein:
the therapeutic composition is adapted for delivery to a patient when the therapeutic composition is at a refrigerated temperature in a range of from 1°C to 10°C; and
when the therapeutic composition is at the refrigerated temperature, it is in the form of a flowable medium with each of the N-acetylcysteine and the poloxamer 407 dissolved in the water.

143. The therapeutic composition of Claim 142, comprising from 0.1 weight percent to 25 weight percent of the N-acetylcysteine.

145. The therapeutic composition of Claim 143, comprising from 10 weight percent to 20 weight percent of the poloxamer 407.

146. The therapeutic composition of Claim 143, comprising up to 10 weight percent of the N-acetylcysteine.

147. The therapeutic composition of Claim 143, comprising about 10 weight percent of the N-acetylcysteine.

148. The therapeutic composition of Claim 147, comprising from 10 weight percent to 20 weight percent of the poloxamer 407.

149. The therapeutic composition of Claim 143, wherein when the therapeutic composition is at a temperature of 2°C the therapeutic composition has sufficient fluidity for use as a mouthwash that can be swished in the oral cavity.

150. The therapeutic composition of Claim 143, wherein when the therapeutic composition is at a temperature of 2°C the viscosity of the therapeutic composition is no larger than 60 cP.

151. The therapeutic composition of Claim 143, wherein the carrier liquid is water.

152. The therapeutic composition of Claim 143, wherein the carrier liquid comprises, in addition to the water, at least one component selected from the group consisting of ethanol and a polyol.

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APPENDIX E
TO
DECLARATION
OF
ANTONY JAMES MATHEWS

Summary Of Viscosity Tests On Example Compositions

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Example 1: Viscosity Behaviors of Formulations Comprising 26% Lutrol® F127, 50% water and 24% Ethanol:

Two 100 gram formulations with the same composition of Lutrol® F127: ethanol: water (26:24:50 w/w) were prepared by the different methods as described below. Lutrol® F127 is a registered trademark of BASF Corporation, and is a pharmaceutical grade of Pluronic F127, a poloxamer 407.

Preparation of Formulation #1: 26g of Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF), 24g ethanol (200 Proof anhydrous, 99.5%, Acros) and 50g water (RO water, 18 Megaohm.cm⁻¹ resistance) were added to a bottle and then cooled on ice. Additionally, the formulation was mixed vigorously with a magnetic stirrer and stir bar, and by shaking the bottle. This formulation became homogenous within a few minutes of mixing.

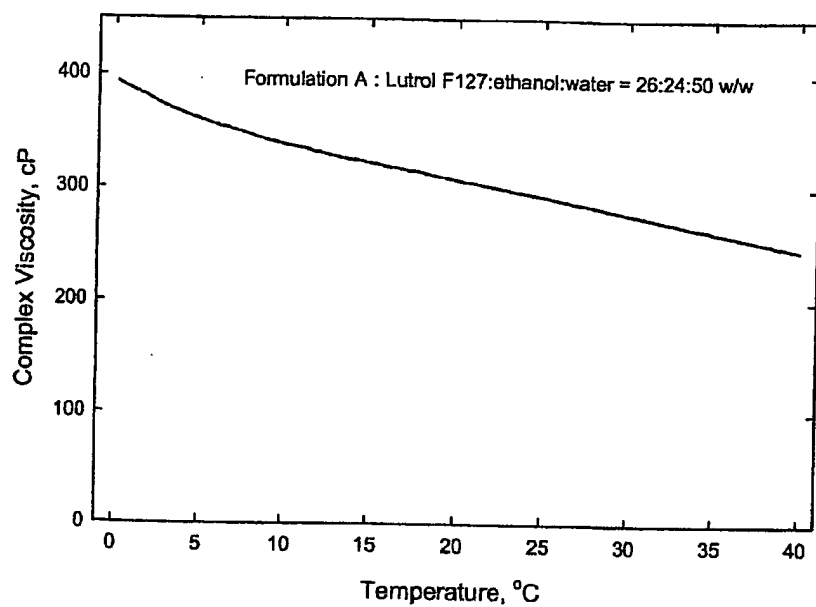
Preparation of Formulation #2: A stock solution of 34.2% w/w Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF) was prepared in water (RO water, 18 Megaohm resistance). To prepare this stock solution, 1316g of water was cooled on ice and then 684g Lutrol® F127 was added with mixing by an overhead mechanical stirrer for 2 hours. After mixing, the stock solution was stored at 4 °C overnight to allow the foam to break down. This process yields approximately 2000g of stock solution. 76g of this stock solution thus contained 26 g of Lutrol® F127 and 50g of water.

Formulation 2 was then prepared by adding 24g of ethanol to 76g of the cold stock solution. The composition was mixed using a magnetic stirrer and stir bar. The formulation immediately formed a homogeneous solution, and was stored at 4 °C.

Analysis: Both formulations 1 and 2 appeared physically identical regardless of their method of preparation and are collectively referred to as Formulation A for the following rheological analysis. The analysis was performed using TA Instruments AR500 Rheometer. A temperature ramp oscillation experiment was implemented to observe viscosity behavior as a function of temperature from 0 to 40 °C.

Results: Figure 1 illustrates thermal viscosity behavior measured for Formulation A between 0 °C and 40 °C. Formulation A does not exhibit reverse-thermal viscosity behavior between 0°C and 40 °C. Figure 1 demonstrates that the viscosity of Formulation A steadily decreased from 400cP at 0 °C to 250cP at 40 °C.

Figure 1: Viscosity Behavior of Formulation A



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Example 2: Viscosity Behaviors of Formulations Comprising 26% Lutrol® F127, 50% water and 24% Propylene Glycol:

Two 100 gram formulations with the same composition of Lutrol® F127: propylene glycol: water (26:24:50 w/w) were prepared by the different methods as described below. Lutrol® F127 is a registered trademark of BASF Corporation, and is a pharmaceutical grade of Pluronic F127, a poloxamer 407.

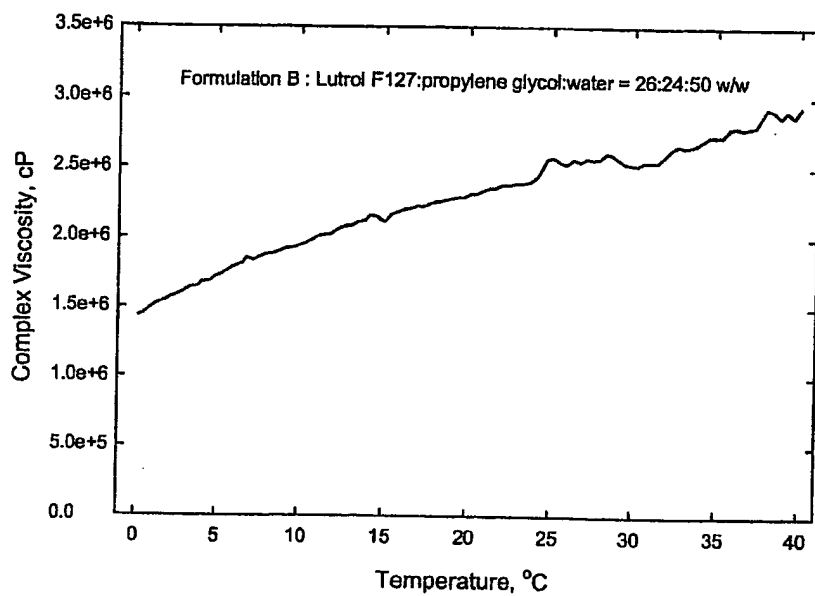
Preparation of Formulation #3: 26g of Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF), 24g propylene glycol (USP grade, Fisher) and 50g water (RO water, 18 Megaohm.cm⁻¹ resistance) were added to a bottle and then cooled on ice. Additionally, the formulation was mixed vigorously with a magnetic stirrer and stir bar, and by shaking the bottle. This formulation required storage at -20 °C for 48 hours before becoming homogenous.

Preparation of Formulation #4: A stock solution of 34.2% w/w Lutrol® F127 (National Formulary pharmaceutical grade, BASF) was prepared in water (RO water, 18 Megaohm.cm⁻¹ resistance) as described in Example 1. 76g of the stock solution thus contained 26g of Lutrol® F127 and 50g water. Formulation 4 was then prepared by adding 24g of propylene glycol to 76g of the cold stock solution. The formulation was mixed using a magnetic stirrer and stir bar. Formulation 4 required storage overnight at -20°C before it became homogenous.

Analysis: Both formulations 3 and 4 appeared physically identical regardless of their method of preparation and are collectively referred to as Formulation B for the following rheological analysis. Analysis was performed using TA Instruments AR500 Rheometer. A temperature ramp oscillation experiment was implemented to observe viscosity behavior as a function of temperature from 0 to 40 °C.

Results: Figure 2 illustrates thermal viscosity behavior measured for Formulation B between 0 °C and 40 °C. The viscosity for Formulation B did exhibit reverse-thermal viscosity behavior, with the viscosity of the composition increasing from 1,400,000cP at 0 °C to 3,200,000cP at 40°C. Figure 2 illustrates that at 25°C the viscosity of Formulation B is approximately 2,500,000cP, or about 350 times greater than the maximum viscosity of 7000cP permitted by Dobrozsi et al. for the compositions of their pourable liquid vehicle.

Figure 2: Viscosity Behavior of Formulation B



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Example 3: Viscosity Behavior of a Formulation Comprising 26% Lutrol® F127, 37.1% water and 36.9% Ethanol:

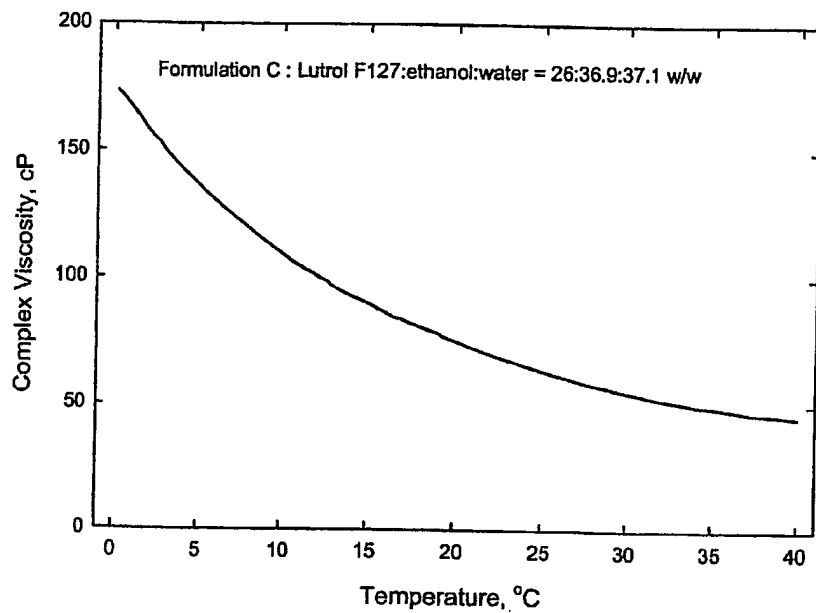
A 100 gram formulation with the composition of Lutrol® F127: ethanol: water (26:36.9:37.1 w/w) was prepared as described below. Lutrol® F127 is a registered trademark of BASF Corporation, and is a pharmaceutical grade of Pluronic F127, a poloxamer 407.

Preparation of Formulation #5: 26g of Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF), 36.9g ethanol (200 Proof anhydrous, 99.5%, Acros) and 37.1g water (RO water, 18 Megaohm.cm⁻¹ resistance) were added to a bottle and then cooled on ice. Additionally, the formulation was mixed vigorously with a magnetic stirrer and stir bar, and by shaking the bottle. This formulation became a clear homogenous solution within a few minutes of mixing and was stored at 4°C.

Analysis: The rheological analysis of this formulation was performed using a TA Instruments AR500 Rheometer. A temperature ramp oscillation experiment was implemented to observe viscosity behavior as a function of temperature from 0 to 40 °C. For rheological analysis, this formulation is referred to as Formulation C.

Results: Figure 3 illustrates the thermal viscosity behavior measured for Formulation C between 0 °C and 40 °C. Formulation C does not exhibit reverse-thermal viscosity behavior between 0°C and 40°C. Figure 3 demonstrates that the viscosity of Formulation C decreased steadily from 175cP at 0 °C to ca. 50cP at 40 °C.

Figure 3: Viscosity Behavior of Formulation C



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Example 4: Viscosity Behavior of a Formulation Comprising 26% Lutrol® F127, 37.1% water and 36.9% Propylene Glycol:

Two 100 gram formulations were prepared with the composition of Lutrol® F127: propylene glycol: water (26:36.9:37.1 w/w) by the different methods as described below. Lutrol® F127 is a registered trademark of BASF Corporation, and is a pharmaceutical grade of Pluronic F127, a poloxamer 407.

Preparation of Formulation #6: 26g of Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF), 36.9g propylene glycol (USP grade, Fisher) and 37.1g water (RO water, 18 Megaohm.cm⁻¹ resistance) were added to a bottle and then cooled on ice. Additionally, the formulation was mixed vigorously with a magnetic stirrer and stir bar, and by shaking the bottle. This formulation was stored at -20 °C for at least 2 weeks with occasional vigorous mixing, but never became homogeneous and large particles of Lutrol® F127 remained apparent.

Preparation of Formulation #7: 26g of Lutrol® F127 (Prill, National Formulary pharmaceutical grade, BASF) and 37.1g water (RO water, 18 Megaohm.cm⁻¹ resistance) were added to a bottle and then cooled using an ice/salt bath. These formulation components were mixed vigorously using a Silverson L4RTA high shear laboratory mixer equipped with a 3/4" inch tubular mixing assembly and containing a square hole high shear screen. Various mixing speeds were used up to 4,000rpm. After 5 minutes of mixing, 36.9g of propylene glycol was added with vigorous mixing and the formulation was mixed for an additional 10 minutes and then stored at -20°C. This formulation did not become homogeneous within 1 week of storage at -20°C, and a significant amount of solid Lutrol® F127 remained.

Analysis: Both formulations 6 and 7 appeared physically very similar regardless of their method of preparation and are collectively referred to as Formulation D for the following comments. Analysis of Formulation D was not attempted because it failed to form a homogeneous state.

**APPENDIX C
RELATED PROCEEDINGS**

None.